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THE SOCIAL INCIDENCE OF RHEUMATIC HEART DISEASE. A STATISTICAL STUDY IN NEW HAVEN SCHOOL CHILDREN. By JOHN R. PAUL, ELIZABETH R. HARRISON, R. SALINGER and G. K. DEFOREST 301

RECURRENCES IN PNEUMOCOCCUS PNEUMONIA. By MAXWELL FINLAND, M.D., and ALEXANDER W. WINKLER, M.D. 309

THE CYTOLOGY OF PLEURAL EFFUSIONS IN PNEUMONIA STUDIED WITH A SUPRAVITAL TECHNIQUE. By T. F. McNAIR SCOTT, M.R.C.P. (LONDON), and MAXWELL FINLAND, M.D. 322

THE OCCURRENCE OF MYELOCYTES IN THE PERIPHERAL BLOOD IN LOBAR PNEUMONIA. By D. J. STEPHENS, M.D. 332

EVANESCENT EFFECT OF INTRATIBIAL INJECTIONS OF BACILLUS WELCHII TOXIN IN RABBITS. By LEONARD J. GOLDWATER, M.D., JOSEPH E. CONNERY, M.D., and HARRY HEIMANN, M.D. 339

LACK OF EFFECT OF LIVER TREATMENT ON THE CIRCULATING RECTICULOCYTES IN THE PIGEON. By HARRY HEIMANN, M.D., JOSEPH E. CONNERY, M.D., and LEONARD J. GOLDWATER, M.D. 343

SPONTANEOUS RUPTURE OF THE HEART SIMULATING SURGICAL ABDOMINAL DISEASE. By HARRY A. SALZMANN 347

ENLARGEMENT OF THE HEART DUE TO ABNORMAL GLYCOGEN STORAGE. IN VON GIERKE'S DISEASE. By WILLIAM ANTOPOL, M.D., JULIUS HEILBRUNN, M.D., and LESTER TUCHMAN, M.D. 354

THE EFFECT OF ELEVATED METABOLISM ON THE HEART OF FRIZZLE FOWL. II. INCREASED RATIO OF HEART TO BODY WEIGHT. By ERNST P. BOAS and WALTER LANDAUER, PH.D. 359

FAMILIAL CLEIDO-CRANIO DYSOSTOSIS. By JULIANNA R. TATUM, M.D. 365

SYMPATHOGONIOMA OF THE ADRENAL. By H. LEBARON PETERS, B.A., M.D., and BENJAMIN HORN, B.S., M.D. 372

THE TREATMENT OF BICHLORID OF MERCURY POISONING: A STUDY OF 46 CASES. By WILLIAM B. PORTER, M.D., and C. E. SIMONS, M.D. 375

A STUDY OF AURICULAR FIBRILLATION FOLLOWING OPERATIONS FOR GOITER. By A. CARLTON ERNSTENE, M.D., and BERT E. MULVEY, M.D. 382

THE ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY INJURIES OF VARIOUS PARTS OF THE VENTRICLE. By HERMAN KOREY, B.S., and LOUIS N. KATZ, M.D. . . . 387

ARTERIOVENOUS FISTULA OF THE RENAL VESSELS. By EDWARD W. HOLLINGSWORTH, M.D. 399

LARGE DOSES OF TUBERCULIN IN TESTING GUINEA PIGS INOCULATED FOR DIAGNOSTIC PURPOSES. By THOMAS B. MAGATH, M.D. 403

SO-CALLED "PRIMARY" TUBERCULOSIS OF MUSCLE. By HENRY MILCH, M.D., F.A.C.S. 410

INDEX TO PHYSICIAN'S SUPPLIES ADV. PAGE 34

Contents continued on adv. page 10

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

SEPTEMBER, 1934

ORIGINAL ARTICLES.

THE SOCIAL INCIDENCE OF RHEUMATIC HEART DISEASE.

A STATISTICAL STUDY IN NEW HAVEN SCHOOL CHILDREN.*

BY JOHN R. PAUL,
ASSOCIATE PROFESSOR OF MEDICINE,

ELIZABETH R. HARRISON,
CLINICAL INSTRUCTOR IN PEDIATRICS,

R. SALINGER,
ASSISTANT CLINICAL PROFESSOR OF PEDIATRICS, YALE UNIVERSITY SCHOOL OF MEDICINE,

AND

G. K. DEFOREST,
NEW HAVEN, CONN.

(From the Departments of Medicine and Pediatrics, Yale University School of Medicine.)

IN a previous paper by one of us[1] the attempt has been made to determine the incidence of rheumatic heart disease in a group of University students, and to relate this incidence to their social and economic background. This study was based on the impression that rheumatic fever is a disease which finds its highest incidence among individuals living under poor hygienic and urban conditions, and that these conditions are usually an expression of poverty. In England, for instance, rheumatic fever has been considered as a disease "of children of the artisan class"[2] and statements have been

* The expenses of this investigation have been defrayed by a grant from the Milbank Memorial Fund for the study of Rheumatic Fever.

made that: "Although technically the rheumatic infection may not be a 'poverty disease' in that its frequency does not seem to follow absolutely the variations in degree of poverty, yet nothing is more certain than that it is a disease of the poorer classes;"[2] also that "No disease has a clearer cut 'social incidence' than acute rheumatism, which falls perhaps thirty times as frequently upon the poorer children of the industrial town, as upon the children of the well-to-do."[3] Few statistics have been collected upon this point in the United States, probably because sociologic data of this type are more difficult to obtain here than in England, in that distinctions between the different classes are not so clearly defined in this country. The few observations from the United States include those of Faulkner and White,[4] who obtained data from colleges and private schools, and concluded that rheumatic infections and rheumatic heart disease were relatively less common among this well-to-do group. Swift[5] states that, "apparently, poverty, malnutrition, and unhygienic surroundings furnish the most favorable soil for the development of this infection. Many cases are seen, however, among well-to-do members of society." Coburn[6] has also commented on the lower incidence of rheumatic fever in private patients than in the medical wards of the Presbyterian Hospital in New York City.

In our previous study[1] emphasis was laid upon the fact that the most practical present approach to an estimate of the incidence of rheumatic fever was the determination of the incidence of rheumatic heart disease. This method is not ideal because the incidence of rheumatic heart disease may, for instance, be an indication of the type of therapy to which rheumatic patients are subjected, rather than an expression of the actual incidence of the disease responsible for the cardiac lesion. With this limitation in mind, however, the incidence of rheumatic heart disease was determined in a group of 8000 Yale University students. This group represented a higher social and economic plane than that from which most large scale statistics of this type have been derived. In it the incidence of rheumatic heart disease was found to be a little more than half that recorded in similar surveys on industrial workers and military recruits. This furnishes added numerical evidence to support the fact that rheumatic heart disease is less common among well-to-do individuals in the United States than among the rank and file, but the statement from England that no disease has a clearer cut "social incidence" was not strikingly reflected in our figures.

As is obvious, these results may be better interpreted when similar data are available from poverty-stricken districts, and for this reason the present study was undertaken. We have now chosen a younger age group than in the first report, namely, children between the ages of 4 and 18 from public, and private schools of New Haven

and its environs. The attempt has been made to determine the incidence of rheumatic heart disease in this juvenile group from the standpoint of poor urban as opposed to good urban living conditions, and from the standpoint of urban as opposed to rural living conditions.

General Data on the Incidence of Rheumatic Heart Disease Among School Children. In reviewing the literature on this topic from different parts of the world, one is struck by the scarcity of accurate data. There are many school surveys in which "heart defects" and "organic heart lesions" have been recorded, but in only a small number has the attempt been made to determine the actual incidence of cardiac defects of rheumatic origin. However, if we assume that 80% of organic heart disease occurring in children under 16 is rheumatic, it is possible to estimate roughly the incidence of rheumatic heart disease from these statistics. This assumption is based upon figures derived from etiological analyses in relation to age, in large groups of cardiac patients in New York City,[7] New England,[8] and Virginia.[9] Its validity is dependent upon another assumption, that these percentages would exist in parts of the world other than those listed above.

In Table 1 figures obtained from various surveys have been listed. In general, and unless otherwise specified, the age group of the different school populations examined ranges between 6 and 15 years. The observed or estimated incidence of rheumatic heart disease (last column of each of the two sections of Table 1), is found to vary from 1.03 to 20.8 per 1000. These variations, as was emphasized in the previous paper,[1] are probably dependent not only upon the children's age, the geographic location and the social character of the population examined, but particularly upon the diagnostic criteria employed.

In one of the best of the American surveys (Boston, 1926[10]) an interesting finding was that in the two most congested urban districts, the percentage of organic heart disease averaged 7 per 1000, while in four less congested districts the average was 4 per 1000. But with the exception of this survey,[10] and another carried out in three counties in the western part of England,[13,14] we are not aware of other school surveys in which the attempt has been made to relate the incidence of rheumatic carditis to social, economic or racial conditions.

Our first effort was to determine whether or not data obtained from the routine physical examination of school children by school physicians of the City of New Haven would be satisfactory for analysis. It was soon apparent that the actual incidence of rheumatic heart disease could not be determined by this approach, but it was possible to obtain data on certain "cardiac defects" in the poorer group of school children which could be compared with similar data from the better-to-do group.

TABLE 1.—THE OBSERVED AND ESTIMATED INCIDENCE OF RHEUMATIC HEART DISEASE IN DOMESTIC AND FOREIGN SCHOOL CHILDREN.

Surveys in the United States.	School population involved.	Organic heart disease per 1000.	Rheumatic heart disease per 1000.
Cincinnati, 1930 (20)	6,960	3.7	2.96*
Boston, 1927 (10)	119,337	5.2	4.5
Philadelphia, 1924 (15)	23,671	6.3	5.04*
Rochester, Minn., 1931 (16)	1,328† (a)	7.0	5.60*
New York City, 1921 (11)	44,000	8.9	7.12*
Chicago, 1923 (17)	158,826	9.0	7.20*
Philadelphia, 1929 (12)	10,333† (b)	9.1	7.6
Florida, Illinois and Missouri, 1929 (18)	17,974	10.0	8.0*
New York City, 1931 (19)	2,691† (c)	11.0	8.8*
New York City, 1918–1922 (17)	1,336,343	13.9	11.12*
Chicago, 1924 (17)	153,671	15.0	12.0*
New York City, 1918 (17)	250,000	16.0	12.8*
Chicago, 1925 (17)	130,260	17.0	13.6*

Foreign surveys.	School population involved.	Organic heart disease per 1000.	Rheumatic heart disease per 1000
Gloucestershire, 1927–1930 (13)	53,501	....	1.03
Bath, 1927–1930 (13)	7,500	....	1.28
Wiltshire, 1927–1930 (13)	43,398	....	1.50
Somerset, 1927–1930 (13)	42,804	....	2.17
Bristol, 1927–1930 (13)	54,673	....	7.72
Transvaal, 1920 (15)	30,000	7.0	5.60*
Glasgow, 1926 (15)	240,000	7.0	5.60*
Hempstead, 1920 (15)	.....	8.2	6.56*
Staffordshire, 1920 (15)	70,138	9.6	7.68*
Aberdeenshire (15)	.....	10.0	8.0*
England and Wales (15)	366,000	10.0	8.0*
Glasgow, 1926 (15)	.....	10.0	8.0*
Edinburgh, 1926 (15)	.....	13.0	10.40*
Birmingham, 1913 (15)	.....	15.0	12.0*
Germany, 1920 (15)	.....	23.0	18.40*
Bath, 1926 (15)	.....	23.6	18.88*
London, 1923 (15)	.....	26.0	20.8*

* Computed on the basis of 80% of "total organic heart disease."

† (a) Ages 11 to 20; † (b) ages 6 to 18; † (c) ages 14 to 17.

*Methods of Examination Employed by School Physicians in the City of New Haven.** The number of children attending public schools in the City of New Haven totals about 34,000 distributed among 65 parochial and public schools. Each year all pupils of the first grade (mostly 5 years of age) and of the fifth grade (mostly 10 years of age) are examined by two school physicians. In recording their data the attempt has not been made by the school physicians to classify heart defects etiologically. As the diagnosis of rheumatic heart disease must rest on certain criteria which do not appear in their records, it has been obviously difficult to estimate its incidence from these figures, but the same method of estimating the rheumatic heart rate from the organic heart rate employed in Table 1, can at least be attempted. Consequently from their data, covering the year 1932, we selected all children with a systolic murmur of the heart thought by school physicians to be "organic" *i. e.*, not a functional murmur. The schools were then divided into two groups. Those attended by children from the more poverty stricken districts of the city were designated as "poorer" schools, and those attended by children from the better districts were designated as "better" schools.

Analysis of the Results of Examinations by School Physicians. Although the diagnostic criteria employed in these examinations by school physicians are limited for our purposes, we believe that the relative incidence of "organic" systolic murmurs (and the fraction of these which may be considered rheumatic) in the two types of schools is of some significance. The latter are shown in Table 2 to be about 1.5 times higher in the "poorer" schools than in the "better" schools.

Results of Our Determinations. In another attempt in which more definite diagnostic criteria were employed, several groups of children were reëxamined by one of us (R. S.). The impossibility of covering large groups by this method is offset by the advantage of using our own diagnostic criteria on the entire group.

Our Own Diagnostic Criteria.—While the diagnosis of clear-cut rheumatic heart disease offers little difficulty, the element of clinical judgment is particularly important in border-line cases. Criteria employed for the diagnosis of doubtful cases of rheumatic heart disease were as follows:

1. A history of rheumatic fever, if present, was regarded as of positive importance in the presence of questionable cardiac signs.

2. Some of the signs which have been regarded as of positive significance are given in the order of their importance. The presence of: (*a*) apical systolic and pre-systolic thrills, or a systolic thrill transmitted to the vessels of the neck. (*b*) Pre-systolic murmurs, aortic diastolic and other mid-diastolic murmurs. (*c*) Cardiac enlargement which could not be explained on any other basis. (*d*) Loud or harsh systolic murmurs best heard at the apex and transmitted laterally.

The diagnosis of congenital heart disease usually rested upon the history, the cardiac findings, the presence of cyanosis, and clubbing of the fingers.

The diagnosis or the interpretation of functional murmurs, of course, offered considerable difficulty. We have followed the view that more definite functional murmurs are generally present at the base of the heart and can be best heard when the patient is prone.

* We are indebted to Mr. Henry J. Schnelle and Miss Margaret Barrett of the Board of Education of the City of New Haven and also to Drs. E. Irene Boardman and Jean Hippolitus for their assistance to us in this work and for the privilege of examining their records.

TABLE 2.—THE INCIDENCE OF SYSTOLIC MURMURS IN CHILDREN FROM "BETTER" AND "POORER" PUBLIC SCHOOLS IN NEW HAVEN.

Type of school.	Grade.*	No. of children examined.	Incidence per thousand. I. Of "organic" systolic murmurs.	Incidence per thousand. II. Of murmurs which may be due to rheumatic heart disease, 80% of I.
"Better"	I	1144	15 13·2	10·5
	V	1123	16 14·2	11·3
"Poorer"	I	1863	36 19·3	15·4
	V	1628	34 20·8	16·6
Total		5758		

It should be emphasized that under the conditions in which our data were obtained, the application of these diagnostic criteria proved difficult. The majority of the cases of rheumatic heart disease encountered among the populations examined represented mild forms, and unfortunately the diagnosis of just such forms as these requires a large element of personal judgment. It was our effort throughout, however, to include only the more definite cases.

Methods of Examination and Character of Populations Examined. In the groups of children subjected to our own examinations, practically all of the diagnoses were made by two individuals both of whom were familiar with the interpretations which the other placed on various physical signs. Thus 98% of the examinations of the urban school children were performed by one of us (R. S.). All the suburban and rural school children were also examined by one of us (E. R. H.).

Urban Public Schools. Two schools, both of them Junior High Schools, attended by pupils between the ages of 12 and 14, were selected. One was attended by pupils from one of the poorest districts in the city, the other by pupils from one of the better districts. Only males were examined, and an average of 8 to 10 minutes was spent on each boy. In the "poor" school 332 boys were examined, and in the "good" school 258.

Urban Private Schools. From 4 private schools 168 children were also examined.† The age group covered that of 5 to 18 years. This group is small but represents a large percentage of the entire private school population of New Haven.

Suburban and Rural Public Schools. This group was drawn from the adjacent town of Hamden in which the total school population is about 5000. One of us (E. R. H.) is the school physician for this district. Cardiac examinations were made on boys and girls during the annual routine examinations of the kindergarten (ages 4 to 5), third grade (ages 8 to 10), and eighth grade (ages 12 to 16). About 80% of the children in this group lived in suburban localities, 20% in rural localities.

Analysis of the Results of Our Examinations. Our incidence determinations of rheumatic heart disease are recorded in Figure 1. It is questionable whether they are actually comparable to those of other surveys, because we are not aware of any survey in which such a careful search for the presence of cases of rheumatic heart disease has been made from the original unselected group. It is our belief, therefore, that our incidence determinations would tend

* The majority of the first grade children were aged 5 years, the fifth grade 10 years.

† We are indebted to the following New Haven physicians for the privilege of examining the private school pupils: Drs. E. T. Wakeman, T. S. Evans, and H. B. Arnold.

to be higher than those recorded in Table 1. Nevertheless, it has not been our major effort to compare our incidence determinations with those of other surveys, but rather to compare the incidence found in different sections of our own group.

From Fig. 1 it will be seen that the highest incidence of rheumatic heart disease (48.1 per 1000) was found among male pupils attending a "poor" urban public school, and that this incidence was 1.5 times higher than that found among a similar group of pupils attending one of the "good" urban public schools (31 per 1000). It was 8 times that of the incidence among the best, or private urban schools in this community. It is unfortunate that this last group, representing as it does but 168 private school pupils, is so

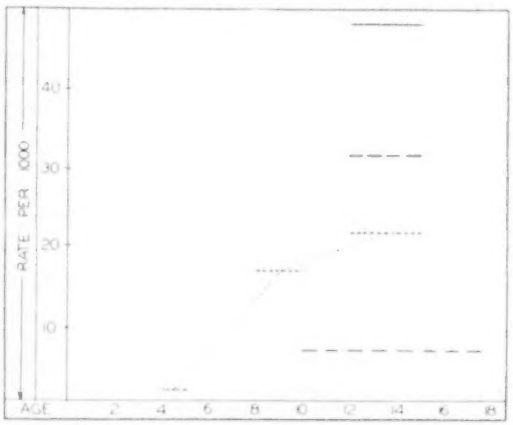

FIG. 1.—The incidence of rheumatic heart disease in public and private urban schools, and public suburban schools.

———— 332 pupils from "poor" urban public school.
— — — — — 258 pupils from "good" urban public school.
- - - - - - - - - - - 2738 pupils from rural and suburban public schools.
Of these 968 = age 12–16; 768 = age 8–10; 1002 = age 4–5.
— · — · — · — · 168 pupils from private urban schools.

small and that their ages cover a wider range than that of the public school pupils. As previously mentioned, however, a large percentage of the private school population in New Haven was included in our examinations and, owing to the small size of the group, limitation to a particular age was impractical.

The incidence determinations on public school children from the rural and suburban groups in which no attempt has been made to divide schools into "poorer" and "better" types is also shown in Fig. 1. The rate among suburban and rural public school children of an age comparable to that of the urban group was found to be about 30% lower than that of the "good" urban public school.

Discussion. Our determinations of the incidence of rheumatic heart disease among poverty stricken and other groups of school

children from New Haven and its suburbs seem to bear out the results of our previous studies on University students. They furnish numerical evidence that in and about this particular city of the United States, rheumatic heart disease found its highest prevalence among the poorest children living in an urban environment. As it has been impossible to measure the actual degree of poverty or affluence in the different groups, or the degree to which those who lived outside the city represented a truly rural group, our figures designating actual heart disease rates are only of relative significance. The most striking finding was that rheumatic heart disease was 8 times as prevalent among pupils attending a school from the poorest section of the city as it was among pupils attending private urban schools from the best residential sections.

One gets the impression from these determinations that in New Haven rheumatic heart disease has a low incidence among the small group of children who represent the homes of greatest affluence, but that it has a high general incidence throughout the remaining 95 or 98% of the population. Thus the high incidence found in the "poorer" public school was but 1.5 times that found in the "good" public school. This is a small difference. To some extent this impression partially reflects the English view previously quoted, that rheumatic fever is a disease of "children of the artisan class."[2]

It is our belief, however, that owing to the nature of the methods employed and the difficulty of applying diagnostic criteria in the border-line cases, our data are still inadequate for broad generalizations on the social incidence of rheumatic heart disease. Our determinations give but a bird's-eye view of the situation. As a further method of increasing knowledge on this subject it has seemed to us that a more intimate study of small communities relating poor and fair living conditions to the prevalence of rheumatic fever is the next step. The report of a study of this latter type will be made in a subsequent paper.

Summary. 1. In an attempt to determine the influence which poverty and urban environments may play as predisposing factors in rheumatic fever, the incidence of rheumatic heart disease has been determined in groups of children between the ages of 5 and 18, attending urban and suburban schools in and about the City of New Haven.

2. Data from the routine examinations of 5758 public school children performed by school physicians suggested that systolic murmurs, presumably of rheumatic origin, were roughly 1.5 times as prevalent among children from the poorer districts than from the better districts of the city.

3. From our own examinations of 758 urban children, the incidence of rheumatic heart disease in a single large public school in one of the poorest districts of the city was found to be 48.1 per 1000. This proved to be 1.5 times as high as that found in a public school in one of the better districts of the city, but 8 times as high as that

found among a smaller group of pupils from urban private schools who came from the best districts in the city.

4. The average incidence of rheumatic heart disease among pupils attending two urban public schools was about twice that recorded among pupils of a similar age group who attended suburban and rural public schools.

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RECURRENCES IN PNEUMOCOCCUS PNEUMONIA.*

By Maxwell Finland, M.D.,

Francis Weld Peabody Fellow in Medicine, Harvard Medical School; Assistant Physician, Thorndike Memorial Laboratory, Boston City Hospital, and Visiting Physician, Pondville Hospital,

and

Alexander W. Winkler, M.D.,

Assistant Resident in Medicine, New Haven Hospital; formerly Assistant Resident Thorndike Memorial Laboratory, Boston, Mass.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School and from the Medical Service of the New Haven Hospital and the Department of Internal Medicine, Yale University School of Medicine.)

A survey of the literature has failed to reveal any considerable body of data from which one may draw any conclusions regarding the actual immunity against reinfection that is conferred upon an

* This study was aided, in part, by a grant given in honor of Francis Weld Peabody by the Ella Sachs Plotz Foundation.

individual as a result of an attack of pneumonia. It is of interest, therefore, to review certain features of a series of 57 cases with repeated attacks of pneumonia from which serologically identified pneumococci were obtained during each of 2 or more attacks.

A history of previous attacks has been noted by various writers in from 13.6 to 31% of pneumonia cases.[1] Many repeated attacks have also been encountered rather commonly.[1,2] As many as 18,[1b] or even 28 attacks,[3] in the same patient have been noted. Among the theories offered to explain this high incidence of recurrences are: (1) That one attack of pneumonia predisposes to another;[1b,1e,4] (2) that there is a local loss of resistance in a lobe once affected by the disease;[1b] (3) that there is an individual constitutional predisposition to pneumonia;[1b,1e] (4) that virulent organisms may persist after recovery and later give rise to reinfection;[5] and (5) that the individuals attacked have a lower level of natural immunity.[6] Other explanations have been based on the recent advances in our knowledge of the biologic specificity of different types of pneumococci[7] and of the immunity resulting from infection or from artificial immunization with these organisms.[8] Thus, Irons[6] intimates that the recurrent attacks are each due to a different type of pneumococcus. Cole [1f] concurs in this opinion but excludes Type III and Group IV cases from this category, the former because of the irregular and low-grade character of the resulting immunity, and the latter because of the heterogenicity of strains within the group.

There are mentioned in the literature only scattered instances of repeated attacks of pneumonia in the same patient with adequate bacteriological data during each attack. Stillman[9] noted a case of Type II pneumococcus pneumonia in a patient who had just recovered from a Type I pneumonia but was meanwhile exposed to a brother who was suffering from Type II pneumonia. Robertson[10] reported a case of Type I lobar pneumonia, probably resulting from direct laboratory infection, which was followed several months later by Type II lobar pneumonia similarly acquired. On the first day of the second attack this patient showed slight bactericidal power for Type II pneumococci in his blood, presumably indicating that he was not unusually susceptible to these organisms. Cole's case with 18 attacks of pneumonia was typed in the last 7 attacks. Type III was obtained during 4 attacks, and Type I, Group IV and Type II atypical in the others.[1f] Cole[1f] and Thomas[11] each reported 1 case of recurrent Type I pneumococcus pneumonia in which serum was given during each attack. Cole's case recurred in the same lobe after 8 months; Thomas' case recurred in a different lobe after 1 month. The latter author also noted 2 cases in which pneumonia recurred but was due to a different type. Cecil[12] and Cole[1f] mention repeated attacks of Type III pneumococcus pneumonia, and the former also speaks of relapses due to the same type occurring after a few days in serum treated cases of Type I pneumonia.

Selection of Cases. The following criteria were used in selecting the cases for this study: (1) Each patient had 2 or more distinct attacks of pneumonia with characteristic physical and roentgenographic findings during each attack. (2) A pneumococcus was isolated and its type identified serologically during each of 2 or more attacks. (3) Each patient was discharged and well before the onset of the succeeding attack, this criterion being used arbitrarily to distinguish "recurrence" from what may be termed "relapse." In several instances, the data relating to additional typical

TABLE 1.—RÉSUMÉ OF CASE HISTORIES OF 20 PATIENTS WITH RECURRENT PNEUMOCOCCIC PNEUMONIA HAVING TYPE I PNEUMOCOCCI IN FIRST ATTACK.

Case number	Sex	Age (years)	Consolidation	Lobes involved	Termination mode and day	Interval from previous attack		Pneumococcus type	Specific serum, kind and day	Remarks (Positive blood cultures, complications, other organisms, etc.)
						Years	Mos			
1	M.	18	L	Rl	C 4	..	..	I	S3	Colored.
		20	B	RlumLl	C 8	2	10	IV	..	
2	M.	49	L	Rl	L 7	..	..	I	..	
		52	L	Ll	L 6	3	3	I	S4	LP = O.
		63	L	Rl	L 8	10	9	VII	..	Mild course.
3	M.	28	L	Lu	C 5	..	..	I	..	
		29	L	Lu	C 5	1	7	I	S4	BC I, colored, serum reactions.
		29	L	Ru	C 4	..	1	I	S3	Sputum = H. Inf., serum reactions.
4	M.	19	L	Rl	L 9	..	..	I	..	BC I.
		22	L	Rl	C10	3	1	IV	H3	Onset 1 day postop. (ether, finger amputation).
5	M.	7	L	Rl	E	..	..	I	..	BC I, PF I, Empyema, rib resection, syphilis.
		18	B	Rl	L16	11	7	XV	..	Rheumatic fever 2 and 1 yr. before; onset with hemoptysis.
6	M.	55	L	Llu	L13	14	..	I	..	Colored, chronic bronchitis, LP–O; 2 previous attacks.
		65	B	RlmLl	D15	9	7	III	..	LP–III, PM, chronic nephritis, arteriosclerosis.
7	M.	27	L	Llu	E	18	..	I	..	Empyema, rib resection (chronic and recurred).
		39	B	RlLl	D 4	11	5	VI	..	Onset 6 days postop. (ether, thoracoplasty) PM, purulent pericarditis (Str. Hem.), healed endocarditis.
8	M.	30	L	Rl	L 8	..	..	I	..	
		41	B	Rm	L15	11	1	III	..	Onset 2 days after fracture 6th and 7th left rib.
9	M.	37	L	Lu	C 8	12	..	I	S5	BC–I, 2 previous attacks.
		48	L	Rmu	C 9	10	10	VIII	..	Pseudocrisis 6th day extended 7th day.
10	M.	45	L	Rl	C 8	3	..	I	..	
		56	L	LluRu	L10	11	..	II	..	BC–II.
11	M.	42	L	Ll	L 7	..	..	I	..	
		50	L	RlLl	L 5	8	9	I	..	Sterile effusion, right.
12	M.	35	L	Lu	C10	6	..	I	..	
		41	L	Ru	C 9	5	10	II	..	BC–II.
13	M.	20	L	Rl	C 7	8	..	I	S6	BC–I, 5 previous attacks.
		20	B	RlLl	C 7	..	1½	I	A6	
14	M.	14	L	Rl	C13	..	..	I	..	
		15	L	Rumd	C10	..	7	IV	..	
		19	L	Rumd	C 7	3	10	VII	..	8 weeks tachycardia.
15	M.	26	L	Ll	C 2	..	..	I	A2	Chronic alcoholism.
		30	L	Rl	C 8	4	5	II	..	
16	M.	33	L	Ll	L13	..	..	I	..	Chronic alcoholism.
		36	L	Ru	C10	2	8	I	..	Mild course.
17	M.	7	L	Rl	C 6	..	..	I	..	
		11	L	Lu	C 6	4	2	II	..	
18	M.	34	L	Rl	L16	..	..	I	S4	BC–I, PF–I, chronic alcoholism.
		35	L	Rl	D 4	1	2	IV	..	H. Inf. in sputum, DT's, PM HB–O.
19	M.	28	L	RlLl	C 9	..	..	I	S5	LP (left and right) = O, H. Inf. and Str. Hem. in sputum, colored.
		38	L	Ll	D12	10	..	II	..	Diabetic coma, empyema, PF = Str. Hem.
20	M.	6	L	Rl	C 9	..	..	I	..	BC–I.
		11	L	Rl	C 7	4	8	III	..	

attacks of pneumonia observed in the hospital are also recorded although bacteriological observations were not made. Standard methods were employed in the isolation and typing of pneumococci.[7a]

Résumé and Analysis of Cases. The more important features of these cases which may be of interest in evaluating local and general immunity are presented in Tables 1, 2 and 3. The features to be considered with respect to each attack are: (1) The character and location of the pulmonary lesion. (2) The duration and mode of termination of the acute disease. (3) The length of the interval between attacks. (4) The bacteriologic findings in the sputum and blood. (5) Specific serum therapy. (6) Complications. (7) Immunologic findings in a few instances where such were made in connection with various other studies.

TABLE 2.—RÉSUMÉ OF CASE HISTORIES OF 18 PATIENTS WITH RECURRENT PNEUMOCOCCIC PNEUMONIA WITH TYPE II OR III IN FIRST ATTACK.

Case number.	Sex.	Age (years).	Consolidation.	Lobes involved.	Termination mode and day.	Interval from previous attack.		Pneumococcus type.	Specific serum, kind and day	Remarks. (Positive blood cultures, complications, other organisms, etc.)
						Years.	Months.			
21	M.	25	L	RIm	C 8	..	..	II	S4	LP = O, serum sickness.
		25	L	RIm	L 8	..	6	I	..	LP = O.
22	F.	13	L	Rm	C 6	..	..	II	..	
		17	L	RILl	C 6	4	6	I	..	
23	F.	20	B	RuLu	C 5	4	0	II	..	Miscarriage (7 mos.) 2 weeks after crisis.
		22	L	Lu	C 8	1	9	I	S6	Pseudocrisis 6th day, 8 mos. pregnant.
24	M.	43	L	Llu	C14	..	..	II	..	
		55	B	RImLlu	D 4	11	4	Pn.	..	Onset after 1 month congestive cardiac failure; PM:HB–O.
25	M.	44	L	Ru	C 8	..	..	II	..	
		45	L	Rl	L 5	..	5	IV	..	
26	M.	14	L	Ll	C 7	..	..	II	..	
		16	L	Lul	C 7	1	11	I	..	
27	M.	13	L	Ll	L 7	..	..	II	..	
		13	B	Ll	L ?	..	2	IV	..	Lung abscess, cleared gradually.
28	M.	39	L	RmLl	L13	..	..	II	A4	BC = II; Pn IV (no Pn II) in sputum after 6th day.
		40	L	Llu	L14	..	9	II	..	
29	F.	48	L	Lul	L 5	..	..	II	A2	BC = II, colored.
		48	L	Rl	D 5	..	3	I	..	BC = I.
30	M.	18	L	Ru	C 4	?	..	II	A4	4 previous attacks.
		19	L	Ru	C 7	1	..	V	..	
31	M.	43	L	Rl	L 5	..	..	II	A3	Sterile pleural effusion, right. Serum sickness.
		44	B	RILl	C 8	..	7	II	..	
32	M.	36	L	Ru	C10	..	..	II	..	Acute and chronic alcoholism.
		38	L	Rl	D24	2	1	III	..	Pericarditis
33	M.	29	L	Ll	C13	..	..	III	..	Otitis media.
		41	L	Rl	C10	11	8	I	S2	
34	M.	44	B	Rl	C 5	..	..	III	..	1 day postappendectomy (ether).
		48	B	RILl	D 4	3	9	I	..	1 day postthyroidectomy (local) for angina pectoris.
35	M.	12	L	Rl	L 7	..	..	III	..	Onset 6th week after pertussis, colored.
		13	L	Lu	L 4	..	2½	II	A3	
36	M.	58	L	Rl	C 6	..	..	III	..	Urine precipitin Pn III.
		62	L	Ll	L 6	4	2	I	S2	Urine precipitin Pn I, serum sickness.
37	M.	66	L	RILl	C 9	30	..	III	..	Left sterile pleural effusion, chronic alcoholism and arteriosclerosis.
		69	B	RILl	C 2	3	2	III	..	
38	M.	59	L	Ruml	E	..	..	III	..	Empyema PF = III.
		62	L	Ru	D26	2	10	IIa	..	Heart block and congestive failure.

TABLE 3.—RÉSUMÉ OF CASE HISTORIES OF 19 PATIENTS WITH RECURRENT PNEUMOCOCCIC PNEUMONIA WITH PNEUMOCOCCUS OTHER THAN TYPE I, II OR III IN FIRST ATTACK.

Case number.	Sex.	Age (years).	Consolidation.	Lobes involved.	Termination mode and day.	Interval from previous attack.		Pneumococcus type.	Specific serum, kind and day.	Remarks. (Positive blood cultures, complications, other organisms, etc.).
						Years.	Mos.			
39	M.	32	L	Rl	L11	..	..	IV	..	Pseudocrisis 6th day.
		35	L	RlmuLl	L 9	3	0	I	..	
40	M.	9	L	Ll	C 6	3	0	IV	..	Left sterile pleural effusion.
		9	L	Ll	C 6	..	5	IIa	..	LP = O.
41	M.	38	L	Rlmu	E	..	..	IV	..	H. Inf. in sputum, bronchopn. Ll (Str. Hem.) 2 months later.
		47	L	Lu	D 7	9	2	I	..	BC = I, PM jaundice.
42	M.	14	L	Ll	C10	..	..	IV	..	LP = O, H. Inf. in sputum.
		15	L	Ll	L11	1	..	IV	..	H. Inf., Str. Hem. and B. muc. caps. in sputum.
		16	L	Rm	C 8	1	..	IV	..	
43	F.	22	L	Ll	L 6	15	..	IV	..	Chronic bronchitis.
		24	L	Ll	L 6	1	8	IV	..	Tonsillitis.
44	M.	12	L	Ll	C 6	3	..	IV	..	Chronic bronchitis, pseudocrisis 4th day.
		13	L	Rl	C 4	..	10	..	..	No satisfactory bacteriology.
		13	L	Ll	C 6	..	1½	II	..	
45	M.	2	L	LlRl	C 6	1	..	IV	..	Chest clear 2d week.
		2	L	LlRl	L 5	..	1	IV	..	Chest clear 3d week, otitis media. | On ward during 3 attacks.
		2	L	Ll	C 5	..	1	IV	..	Chest clear 2d week. | Kept because of ward quarantine.
		2	L	Ll	C 3	..	1	..	..	No satisfactory bacteriology.
46	F.	22	L	Lu	L 6	..	..	IV	..	
		32	L	Rl	L 7	10	6	VIII	..	
47	M.	21	L	RuLl	L12	..	..	IV	..	Colored, syphilis, jaundice.
		31	L	Rl	C 3	9	2	VIII	..	BC = VIII.
48	F.	56	L	Lu	L 9	1	..	IV	..	Hypertension, 2 previous attacks.
		63	L	Lul	D18	7	..	III	..	Delirium, fell from bed and fractured femur 11th day.
49	M.	28	L	Ru	C 9	..	..	..	..	Acute and chronic alcoholism.
		30	L	Ru	C 7	2	2	IV	H3	
		36	L	Rul	L 7	6	..	I	A4	
50	F.	29	L	Rl	C 9	1	..	IV	..	Many previous attacks, asthma; chronic bronchitis.
		37	B	Rl	C 7	7	4	II	..	
51	M.	31	L	Rl	L 8	..	..	IV	..	Asthma and chronic bronchitis.
		39	L	Ll	L10	7	9	I	..	Chronic alcoholism.
52	F.	36	B	Ll	L10	..	..	IV	..	Decompensated rheumatic heart.
		38	B	Rl	L 6	2	..	X	..	Cardiac decompensation.
53	M.	14	L	Ll	C 7	2	..	VII	..	3 previous attacks.
		16	L	Rm	C 7	2	..	Pn	..	
54	M.	40	L	Rl	C15	..	..	VIII	..	Colored, right sterile effusion.
		40	L	Rul	E	..	3	I	A7	Empyema, PF I.
55	M.	12	L	Rl	C 5	..	..	VII	A4	
		13	L	Rl	C 4	..	11	I	A3	
56	F.	22	B	Rl	L 6	..	..	IV	..	
		24	L	Rl	C 5	2	..	I	K4	
57	M.	50	L	Ll	C 8	..	..	IIa	..	Str. Hem. in sputum.
		50	B	RlLl	L16	..	6	IV	..	Str. Hem. in sputum.

EXPLANATORY NOTE. *Tables* 1, 2 *and* 3.

Cases 17, 18, 20, 31, 35, 36, 37, 55 and 57 are from the New Haven Hospital.

Cases 3, 20 and 39 were previously reported by Thomas.[11]

Case 13 was reported by Kohn, L. A. (J. A. M. A., **85**, 1888, 1925) from the Peter Bent Brigham Hospital.

Abbreviations Used Under Various Headings.

Sex: M = male; F = female. *Consolidation:* L = lobar; B = patchy (bronchopneumonia). *Lobes:* R = right; L = left; l = lower; u = upper; m = middle. *Termination:* C = crisis; L = lysis; D = died; E = empyema; "day" = days after onset. *Type:* IV = No agglutination with Type I, II or III; Pn = No agglutination with Types I–XX (incl.). *Serum: Kind:* S = Unconcentrated, homologous type antiserum; H = Huntoon's antibody (Types I, II and III); A = Felton's concentrated antibodies (Types I and II); K = Keyes' chicken serum. *Remarks:* BC = Blood culture (sterile cultures are not noted); O = Sterile; I, II, etc. = Pneumococcus Type I, II, etc.; LP = culture of lung puncture material; PF = Pleural fluid; PM = Postmortem; HB = Heart's blood culture; H. Inf. = Hemophilus influenzæ; Str. Hem. = Streptococcus hemolyticus; B. muc. cap. = Bacillus mucosus capsulatus (Friedländer).

Age, Sex, Color. Most of the patients were adult white males. There were 5 patients under 12 and 7 patients over 50 years of age during the first attack. Nine of the patients in this series were females; 7 of the males and 1 of the females were colored.

Character of the Pulmonary Lesions. (Table 4.) The pulmonary lesion in 72% of the cases was lobar in distribution during each observed attack. There were 3 such attacks in each of 6 patients and 4 in 1 case. In all but 4 of the remaining cases an "atypical" or patchy lesion (bronchopneumonia) was observed only during the recurrence. The 7 cases having the same pneumococcus type (excluding Group IV) in both attacks all had lobar pneumonia in the first attack. The lesion during the recurrence in these cases was lobar in 4 instances and patchy in the others.

TABLE 4.—COMPARISON OF EARLY ATTACKS AND RECURRENCES.

ALL CASES.

Pulmonary Lesion:

In first attack.	In recurrence.	Number of cases.
Lobar	Lobar	41 (72%)
Lobar	Atypical	12
Atypical	Lobar	2
Atypical	Atypical	2

NON-FATAL CASES.

Duration of Acute Disease:

	Number of cases.
Same (± 1 day) in both attacks	23 (45%)
Recurrence 2 or more days longer	11
Recurrence 2 or more days shorter	17

Mode of Termination:

First attack by.	Recurrence by	
Crisis	Crisis	25 } (69%)
Lysis	Lysis	12 }
Crisis	Lysis	8
Lysis	Crisis	7
Crisis	Empyema	1
Empyema	Lysis	1

FATAL CASES.

Case No.	First attack. Mode of termination.	First attack. Complications.	Fatal attacks.
19	Crisis	Str. Hem. in sputum	Diabetic coma; Str. hem. empyema.
23	Crisis	.....	Prolonged congestive heart failure.
31	Crisis	Acute alcoholism	Pericarditis.
33	Crisis	Postoperative	Postop.; Str. hem. pericarditis and mediastinitis.
6	Lysis	.....	Chronic nephritis, arteriosclerotic heart.
18	Lysis	Bacteremia, alcoholism	Delirium tremens.
28	Lysis	Marked bacteremia	Bacteremia.
47	Lysis	.....	Fracture femur.
7	...	Empyema	Postop.; pericarditis; endocarditis.
37	...	Empyema	Heart block, cardiac failure.
40	...	Empyema	Jaundice, bacteremia.

Secondary Pneumonias. In 16 instances the attacks of pneumonia were secondary to conditions other than common colds. These attacks were secondary to operative procedures in 4 instances, congestive heart failure in 5, asthmatic attacks in 4 instances and fractured ribs, pertussis and diabetic coma each in 1 instance. The pulmonary lesion in 9 of these secondary attacks was patchy in character. In addition, 7 of the patients were chronic alcoholics who were more or less under the influence of alcohol at the time of each admission.

TABLE 5.—COMPARISON OF LUNG INVOLVEMENT DURING THE FIRST AND SUBSEQUENT OBSERVED ATTACKS OF PNEUMONIA.*

		Lung involved during recurrence.									
		Right lung.				Left lung.					
	Lung involved during first attack.	Lower.	Upper and / or middle.	Entire.	Total.	Lower.	Upper.	Entire.	Total.	Bilateral.	Total (first attack).
Right Lung	Lower	6	1	2	9	5	2	0	7	6†	22
	Upper and / or middle	2	2	1	5	0	0	0	0	1	6
	Entire	0	1	2	3	0	1	0	1	0	4
	Total	8	4	5	17	5	3	0	8	7	32
Left Lung	Lower	6	2‡	0	8	3	1	1	5	2‡	15
	Upper	1	4‡	0	5	0	1	1	2	0	6
	Entire	1	0	0	1	0	0	0	0	3	4
	Total	8	6	0	14	3	2	2	7	5	26
	Bilateral	1	0	0	1	2	1	1‡	4	2‡	7
	Total (recurrence)	17	10	5	32	10	5	3	19	14	65

* In this table all the observed attacks are included.
† 2 cases with same type both attacks.
‡ One of these cases had the same type during both attacks.

Location of the Pulmonary Lesion. In Table 5 are shown the numbers of cases having various lobes of the lung involved during the first observed attack, and these are correlated with the location of the lesion during the recurrence. If due allowance is made for the small numbers with which we are dealing, it may be said that the various lobes were involved with the usual frequency during both the early attacks and during the recurrences. Furthermore, there was no constant correlation between the site of the initial involvement and that of the reinfection. Thus, among the 32 cases with right-sided involvement during the first attack and

among the 26 cases with the left-side involved in this attack, about the same proportion of cases involved the right and the left lung, respectively, during the recurrent attack. Bilateral lung involvement, however, was twice as frequent during the recurrence. The site of the original lesion was involved during the recurrence in 36 instances (56%). Three of the 7 cases having the same fixed pneumococcus type during 2 successive attacks showed more extensive involvement during the later attack, and in 5 of them the original site was again affected.

Mortality. The death rates in this series are considerably lower than those obtaining in the general run of cases.[14] They are shown in Table 6. Survival, however, is not the only criterion which differentiates mild from severe infection. Other features may be compared, however, and these may reflect to some extent the character of the different attacks.

TABLE 6.—MORTALITY.

Age in first attack.	Number of cases.	Died in later attack.	Per cent. fatal.
29 or less	31	2	6.0
30 to 49	20	6	30.0
50 or over	6	3	50.0
Total	57	11	19.0
	Number of attacks.	Attacks fatal.	Per cent fatal.
Specifically treated	26*	0	0
Not specifically treated	96	11	11.5
Total	122	11	9.0

* 15 received serum during the first attack and 11 during the recurrence.

Duration of Acute Disease and Mode of Termination. It is interesting to compare the duration of the acute disease and the mode of termination in the different non-fatal attacks. Crisis, for this purpose, is arbitrarily defined as a permanent drop in temperature to below 101° F. with coincident marked alleviation of acute symptoms within a period of 24 hours. A more prolonged subsidence of fever and symptoms is called lysis. In this connection, it is also worth noting the mode of termination of the earlier attacks and some other features in the 11 cases which later ended fatally. These comparisons are shown in Table 4. In general, the successive attacks were quite similar in each individual as regards duration of the acute illness and mode of termination. In the fatal cases where definite complications did not account for such outcome the preceding attack was severe or otherwise complicated. In none of the fatal cases was the recurrence of the same pneumococcus type as the preceding attack.

Interval Between Attacks. (Table 7.) The shortest interval between attacks which were observed and were associated with

serologically identified pneumococci was 4 weeks, the longest interval was 11 years and 8 months, and the average was about 4 years. Of 19 cases recurring within a year, 4 were of the same pneumococcus type. These were each treated with specific antiserum in the first attack. The second attack in these cases occurred 4 weeks, 6 weeks, 7 months and 9 months later, respectively. The average interval between attacks that were of the same pneumococcus type was 28 months.

TABLE 7.—INTERVAL BETWEEN ATTACKS OF PNEUMOCOCCUS PNEUMONIA.

Interval.	Number of cases.	Number with same type.*
Less than 2 months	5	2†
2 to 6 months	6	0
7 to 12 months	8	2‡
1 to 3 years	12	1
3 to 5 years	10	1
5 to 10 years	10	1
10 or more years	9	0
Total	60	7

* Excluding cases with Group IV on successive occasions.

† Both serum treated Type I cases, interval of 4 and 6 weeks, respectively.

‡ Both Type II cases, interval of 7 and 9 months, respectively; each serum treated during first attack.

Average interval between attacks in all cases—approximately 4 years.
Average interval between attacks due to same type—2½ years.

TABLE 8.—COMPARISON OF TYPES OF PNEUMOCOCCI RECOVERED DURING EARLY ATTACK AND DURING RECURRENCE.*

Type at first observed attack.	Type during recurrence. I.	II.	III.	Others.	Total (first attack).	Distribution per cent (first attack).
I	4^2	5^2	3	8^4	20^8	33
II	5^2	2^2	1	4^1	12^5	20
III	3	1	1	1	6	10
Others	7^2	2	1	12	22^2	37
Total (recurrence)	19	10	6	25	60	100
Per cent distribution (recurrence)	32	17	10	42	100	.....

* Exponents represent the number of cases receiving specific serum during earlier attack.

Type II atypical included in Group IV.

Pneumococcus Types. The numbers and percentages of cases from which the various types of pneumococci were obtained during the early and the succeeding attacks are correlated in Table 8. When due allowance is made for the small numbers concerned, the distribution of cases among the various types during the early

attacks and during the recurrences is very similar to that found in any large series of cases of pneumococcus pneumonias. There was obviously no correlation between the types obtained during the different attacks. For example, the 20 cases with Type I pneumococci during the first attack had about the usual distribution of types during the succeeding pneumonia and, conversely, the 19 patients having Type I pneumococci in the later attack were similarly distributed among the different types during the first attack. The same was true for the other types.

The same type was isolated during the later attack in 4 of 13 cases in which homologous type antiserum had been given for a previous attack. It will be noted from Tables 1 and 2 that in 3 of these 4 treated cases (Cases 13, 27 and 36) the original lobe was involved during the recurrence.

Only a small proportion of the Group IV pneumococci in the present series were definitely classified according to the new sero-serologic types of Cooper.[7] In 5 of the 12 cases, however, in which pneumococcus types other than I, II or III were obtained during successive attacks, the finding of an atypical Type II, Type VIII (atypical III) or absence of agglutination for the original type indicated that the two attacks were probably associated with different types. Other organisms, chiefly hemolytic streptococci and influenza bacilli, were isolated in some instances in addition to the pneumococcus.

Bacteremia. In most of the cases in this series blood cultures were made on one or more occasions during each acute attack. Positive cultures were obtained in 9 of the 47 cases (19%) in which cultures were made during the first attack. In the latter attack 6 of 52 cases (12%) yielded positive blood cultures, and 3 of these 6 cases ended fatally. Only 1 patient had a positive blood culture during successive attacks, the latter one proving fatal. In most large series of cases bacteremia is usually demonstrated in about 30% of cases.[14a]

Specific Therapy. Some kind of specific antipneumococcus serum was used in the treatment of 26 attacks in this series. (See Tables 1, 2, 3 and 7.) In 15 cases the serum was given during the first attack, and these alone are of interest for the purpose at hand. These 15 cases fall into 3 groups. In the first group are 7 patients in whom the recurrence was associated with a pneumococcus of a type not contained in the antibody administered. In the second group are 4 patients who were given a polyvalent antibody for the first attack and who had a recurrence with a pneumococcus type included in this antibody but different from the type causing the original infection. In the third group are 4 patients receiving homologous antiserum and having recurrences with the same type of pneumococcus. Cases 3 and 13 received homologous antiserum for a

Type I infection and had a recurrence with the same type 4 and 6 weeks later, respectively; and Cases 27 and 30 each had Type II pneumonia, were given concentrated Type I and Type II antibodies (Felton) during the height of the disease and had recurrences with the same type 9 and 7 months later, respectively. The pulmonary lesion in Cases 13, 27 and 30 was somewhat more extensive during the recurrence, but the site of the original attack was also affected during the recurrence. In Case 3 the later attack involved a different lobe.

Immunity Reaction. Data concerning antibodies are available in 7 of the patients, including 4 who were treated with serum during the first attack. All had antibodies for the homologous type after each attack. Only 1 patient (Case 29) had antibodies for the original type of pneumococcus at the time of the recurrence, 1 year later. In Case 27 the homologous Type II antibodies disappeared within 2 weeks after serum treatment, and pneumonia due to the same type recurred in 9 months. In Case 16 there was a spontaneous recovery with a high titer of homologous (Type I) antibody persisting for several months, but pneumonia recurred with the same type about 3 years later.

Comment. The cases in this study were included, after a search of more than 5000 "typed" cases in two large hospitals, because they were the only ones found to satisfy the criteria set down. No attempt was made to determine the exact incidence of previous infections in the entire group of pneumonia patients in these clinics because it was felt that the histories could not always be considered reliable and no satisfactory information could be obtained regarding the details of such illness, especially in regard to etiology. It is interesting to note, however, that among 1000 consecutive "typed" cases of pneumococcus pneumonia in which data on this point were recorded, a history of one or more attacks before admission was noted in 16.5%. Indeed, in the present series, 6 cases were observed in 3 attacks, 1 in 4 attacks and 13 (23%) gave a history of one or more attacks of pneumonia previous to the first entry to the hospital. These figures correspond to those recorded by other writers.[1] A review of the case histories of 1000 consecutive medical patients treated for diseases other than pneumonia, however, revealed that 14% of these individuals gave a history of one or more attacks of pneumonia prior to entry.

With respect to the character of the different attacks, most of the data presented seems to indicate that, in general, the successive attacks, considered as a group, were very similar. The duration of the disease and mode of termination were similar. Bacteremia was nearly as frequent, and the distribution of the sites of the lesion and of the different pneumococcus types was very similar in the early and in the later attacks. Among the fatal cases, either there

was some other important contributing factor in the fatal attack or the preceding attack was also unusually severe.

The group of later infections did differ, however, in two important respects: (1) Bilateral involvement was twice as frequent; and (2) the instances of bronchopneumonia occurred chiefly in the last attack. With respect to the former it may be noted that in 14 of the 18 instances where there was more extensive involvement in the later attack, the site of the original infection was again involved. This, and the fact that in 16 other instances the same lobe was involved in successive attacks, indicates that there is certainly no increase in local resistance.

With regard to the instances of "atypical" or bronchopneumonia, two points may be mentioned which suggest that this type of lesion may indicate a greater susceptibility during the later disease. First, the types of pneumonia generally associated with such lesions are frequently avirulent for animals, in contrast with the highly virulent pneumococci, usually Types I and II, associated with typical lobar pneumonia.[3] In a recent study[14c] it was further shown that where the same type of pneumococcus causes both lobar pneumonia and bronchopneumonia, the cases with the latter type of involvement are more often secondary to other diseases and have a much higher fatality rate, presumably indicating a lower resistance brought about by the primary disease.

In only 4 instances was there any evidence suggesting that persistence of the original virulent organisms may have accounted for the recurrence. These were the 4 cases in which reinfection with the same type occurred within a year. In 1 of these cases, however, careful study of the sputum on several occasions after the first few days of the original infection failed to reveal the Type II organism originally in the sputum and blood and which was again recovered from the sputum at the time of the second attack.

That the specific humoral immunity resulting from reinfection or immunization with pneumococci is of brief duration is well recognized. Occasional instances of persistent antibodies for a year or more, such as was noted in Case 29, have been observed before.[15] The measures of immunity usually employed, however, are not very delicate, and the interpretation of these immune reactions in terms of actual susceptibility in man is not clear. In the only case in this series where immunity to any type was demonstrated early in the disease, the infection was caused by another type. The demonstration of circulating type-specific antibodies, or even of tissue immunity, if the specific skin reactions may be interpreted as such, does not preclude later infection with the same pneumococcus type. Nor do the present data indicate that specific serum treatment seriously alters the future susceptibility to the same type,

although specific antibodies can be demonstrated for shorter periods in such cases as compared with those recovering spontaneously.[16]

Summary and Conclusions. In this paper is presented a study of 57 cases having recurrent attacks of pneumonia associated in each instance with serologically identified pneumococci.

An analysis of the major features of the early attacks and of the recurrence fails to indicate any marked change in the local or type-specific susceptibility.

The distribution of types of pneumococci and of the sites of the pulmonary lesion, both in the early and the late attacks, was very si nilar to that usually observed in pneumococcus pneumonia.

A larger number of cases had more extensive and "atypical" lesions during the recurrent attack.

Specific serum therapy in the first attack in general had no marked effect on the character of the recurrence. Early recurrences with the same type, however, are more frequent among the serum-treated cases.

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THE CYTOLOGY OF PLEURAL EFFUSIONS IN PNEUMONIA STUDIED WITH A SUPRAVITAL TECHNIQUE.*

By T. F. McNair Scott, M.R.C.P. (London),
INSTRUCTOR IN PEDIATRICS, HARRIET LANE HOME, JOHNS HOPKINS HOSPITAL, BALTIMORE, MD.,

AND

Maxwell Finland, M.D.,
FRANCIS WELD PEABODY FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL, AND ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.)

The observations of Gay and his associates[1–5] have indicated that the type of cell present in the pleural exudate, experimentally induced in rabbits, has a determining influence on the establishment and the course of local streptococcic infections, and possibly, also, on those with the pneumococcus.[6] In the course of pneumococcic pneumonia in man, there is always some pleural reaction, and actual effusion may be present in a large percentage of cases. In some instances, such an effusion remains sterile and is absorbed; in others, it becomes infected and may require intervention. A study of such effusions, at various stages of pneumonia, was undertaken in the hope that information might be obtained in regard to their probable course and outcome. The immunologic characteristics of such fluids have already been reported by one of us.[7] The present study concerns the cytology of such fluids as revealed by a supravital technique which gives a clear differentiation of the cells and also yields information regarding their viability and activity.

The presence of pleural effusion in pneumonia has long been recognized.[8–10] Its frequency has been indicated by many observers,[11–13] some of whom differentiated between the benign serofibrinous fluids and the serious purulent type.[14–19] Studies of the cells in such fluids were made by Quincke[20] and by Ehrlich,[21] the latter using stained preparations. Widal and his associates,[22,23] however, were the first to indicate the diagnostic significance of the cytological formula. They recognized the presence of "macrophages" and lymphocytes late in pneumonic effusions which remained sterile. Similar observations were made in occasional cases by Dopter,[24] and by other writers[25,26] in the pneumonias of infants by Ylppö[27] and in an effusion of typhoid fever by Pepper.[28] Eosinophilia, up to 65%, has been noted late in pneumonic effusions.[29–32] Studies of exudates, including occasional pneumonic pleural fluids, with the aid of vital stains have been reported recently by Uijeyonahara[33] who used soda carmin and by Hickling[34] who used neutral red.

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Materials and Methods. A total of 53 fluids, 32 sterile and 21 infected, were obtained from 32 patients with clinical and roentgenographic evidence of lobar pneumonia. Pneumococci were cultured from the sputum or blood of each patient. With one exception (Case 25, in which the fluid became secondarily infected during an hemolytic streptococcus septicemia that complicated convalescence), the same type of pneumococcus was recovered from each infected fluid as was originally obtained from the sputum or blood. Agglutinating sera, Types I to XX (Cooper[35]) were used to type the pneumococci. Specific serum (Felton) was used in the treatment of 9 of the patients. Novocain in a 1 to 2% solution was used for local anesthesia. The hydrogen-ion concentration was obtained with the use of indicators by comparing with standard buffer solutions (Clark[36]).

The fluids varied in appearance from clear and straw-colored fluids which clotted readily, and which were called "sero-fibrinous" to hemorrhagic fluids and frank pus. In the latter there was little doubt as to the nature of the fluid, but in those which were seropurulent it was impossible to tell grossly whether or not the fluid was infected.

A total leukocyte count and a differential count of 100 to 400 cells was made as soon as possible after the fluid was withdrawn. In some instances accurate total counts were not made due to the rapid clotting of the fluids. The supravital technique employed was that described by Forkner[37] which is a modification of the methods of Simpson[38] and Sabin [39] and their associates. It consists essentially in a study of the reaction of the various cells to two anilin dyes, neutral red and Janus green, which preserve their activity and undistorted morphology. Neutral red is an indicator which stains the specific granules and vacuoles different shades from red to yellow depending on whether they are acid or alkalin. Thus, the granules of eosinophils, which are essentially alkalin, stain a yellowish color, while those of a basophil, which are essentially acid, stain bright red. Janus green, in the concentration used, is a specific stain for mitochondria. These vary with different cells and also with the age of the cells, being coarse in lymphocytes and fine in monocytes and tending to be more numerous in the more immature cells. Essentially the cells in these fluids were similar to those described in the blood or other tissues by the originator and the elaborators of the method.[38,39] Some of the characteristics of the cells, especially as they differ from those found in blood, will be discussed below. Examples of the appearance of most of the cell types encountered are shown in Plate I.

Cytologic Findings. The significant data relating to each of the patients and to the fluids are given in Table 1. These findings will be summarized in connection with the discussion of the various types of cells encountered.

Polymorphonuclear Neutrophils. Four different forms were encountered: (1) active; (2) rounded; (3) degenerating and (4) non-motile. The *active* forms were motile and had yellowish specific granules similar to those found in the cell of blood. They differed from the latter in 3 respects. (1) The "specific granules" stained poorly in many instances. (2) Red "segregation granules" were noted. These were, in reality, vacuoles filled with acid staining products of metabolism and were similar to the ones noted by Sabin[39] in the blood neutrophils in a case of pneumonia. (3) Large numbers of "refractile globules" accumulated in the cytoplasm. Such heavily loaded cells moved sluggishly. While these cytoplasmic changes may represent increased phagocytic activity, they probably also

indicate cell damage, since similar refractile globules appear in dead leukocytes. The granules may be due to the inability of the cells to absorb some of the ingested materials but more probably indicate beginning degeneration. The *rounded* forms were similar to those found in blood. They probably represent a state of temporary or permanent inactivity. The *degenerating* and *dead* forms showed a characteristic reaction to neutral red. The former, if still living when the stain was applied, took up the dye very quickly, the nucleus staining a diffuse red, indicating that the cell died soon after being stained. The dead cells were rounded and failed to stain. Their cytoplasm showed a few refractile granules and the nucleus had a ground-glass appearance and formed a round swollen mass in the center of the cell. The *non-motile* cells appeared the same as similar cells in blood, but they were seen only rarely. Hickling failed to observe them in any of his cases. According to Sabin[39] they represent cells about to die a natural death. Their rare appearance in these fluids may depend on their lack of motility. All of these forms were seen in varying proportions in the majority of the effusions studied.

The predominance of neutrophilic polymorphonuclear cells in pleural fluids accompanying acute infections has been noted by all observers.[22–28] In the present cases these cells constituted from 80 to 100% of leukocytes in the early uninfected fluids and practically 100% in all the infected effusions. In fluids which remained uninfected, the proportion of these cells tended to fall rapidly, so that after the 8th day they constituted less than 60% of the cells in almost every case; whereas, in those which later became infected they remained at, or rapidly reached, 100% (Fig. 1). In infected fluids the majority of these cells lost their motility and assumed first the rounded, then the degenerating and finally the dead form.

Experimentally, the rounded forms and the faintly staining active forms could be induced in normal blood by mixing it with equal parts of 2% novocain solution before staining. The presence of novocain, however, probably did not account for the findings in the fluids, inasmuch as only small amounts of novocain in separate syringes were used for anesthesia and care was taken not to introduce any into the pleural cavity.

Eosinophils. These were very similar in appearance to blood eosinophils. They were less motile than the neutrophils and con-

LEGEND FOR PLATE I.

Pencil drawing of cells from pleural fluids as they appear supravitally stained with neutral red and Janus green. (× 1400.) 1, rounded polymorphonuclear neutrophil; 2, active polymorphonuclear neutrophils; 3, active polymorphonuclear neutrophil with many refractile granules; 4, mesothelial cell; 5, small lymphocyte; 6, monocytes; 7, macrophage, with many red stained vacuoles; 8, macrophage with ingested polymorphonuclear neutrophil but only few vacuoles; 9, erythrocytes.

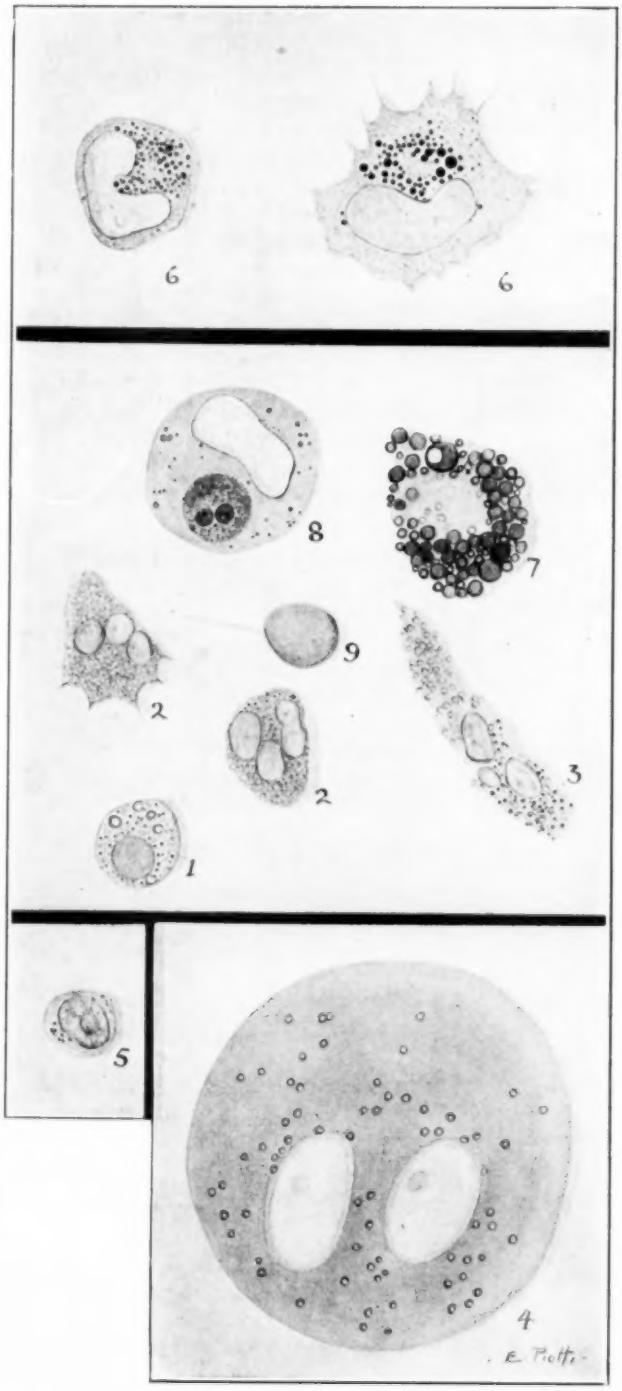

PLATE I.

TABLE 1.—SUPRAVITAL DIFFERENTIAL CELL COUNTS OF PNEUMONIC PLEURAL FLUIDS.

Case number.	Age.	Pneumococcus.	Day of crisis.	Day of puncture.	Amounts withdrawn.	Description of fluid.	Reaction.	Leukocytes per cm.	Polymorphonuclear neutrophils.					Eosinophils.	Lymphocytes.	Monocytes.	Macrophages.	Total monocytes and macrophages.	Mesothelial.	Unclassified.	Erythrocytes.
									Active.	Round.	Degenerating.	Non-motile.	Total.								
	Years.	Type.			cc.		pH.	X10³	%	%	%	%	%	%	%	%	%	%	%	%	
									STERILE FLUIDS.												
						Patients receiving no serum.															
1	21	0	15	1	10	Ser. Sang.	7.4	.....	95.5	0	0	0	95.5	0	0.7	2.5	1.2	3.7	0	0	+++
..	..	..	..	3	15	Ser. Sang.	7.4	60.0	88.3	0	0	0	88.3	0	2.3	4.8	3.0	7.8	1.0	0.5	+++
..	..	..	..	5	30	Ser. Fib.	7.6	16.3	86.0	0	0	0	86.0	1.0	0.5	7.5	2.5	10.0	1.0	1.5	++
2	48	III	5	3	5	Sang.	...	29.3	0	0	96.0	0	96.0	0	0	0	0	0	4.0	0	++++
3	28	III	10	3	10	Ser. Sang.	...	.....	98.0	0	0	0	98.0	0	0	0	2.0	2.0	0	0	++++
..	..	..	..	8	8	Ser. Sang.	...	20.0	54.0	0	0	0	54.0	0	5.0	22.0	12.0	34.0	1.0	2.0	++
4	21	I	5	4	8	Ser. Fib.	8.0	39.1	95.0	0	0	0	95.0	0	0.5	1.0	3.5	4.5	0	0	....
5	16	II	3	4	2	Sang. Pur.	7.4	134.0	78.5	6.0	0	0	84.5	0	2.0	11.0	1.0	12.0	1.5	0	++
6	44	XVIII	11	5	30	Ser. Fib.	7.7	56.0	79.0	18.0	1.0	0	98.0	0	0.5	1.5	0	1.5	0	0	++
..	..	..	..	7	7	Ser. Sang.	8.0	21.9	61.0	8.0	1.0	0	70.0	0.5	0	6.5	18.5	25.0	4.0	0.5	+++
7	8	II	6	5	10	Ser Fib.	...	7.4	42.0	24.0	0	0	66.0	0	4.0	20.0	10.0	30.0	0	0	....
8	35	X	5	5	20	Ser. Fib.	7.8	2.7	68.0	8.0	9.0	0	86.0	0	2.0	5.0	7.0	12.0	1.0	0	++
9	17	I	5	5	20	Ser. Pur.	7.2	3.7	70.5	0	0	0	70.5	0	1.7	13.2	12.2	25.4	1.7	0	++
10	1¼	..	11	8	20	Ser. Pur.	...	40.0	Sheets of monocytes and macrophages, rare polymorphonuclear neutrophil containing fat granules.												+++
11	1½	XIV	11	9	10	Ser. Pur.	...	35.0	35.0	14.0	0	1.0	50.0	1.0	3.0	28.0	16.0	44.0	2.0	0	+
12	49	IX	9	10	10	Ser. Fib.	...	7.4	15.0	2.0	0	0	17.0	0	78.0	1.0	0	1.0	3.0	0	....
13	48	I	10	10	30	Ser. Sang.	8.0	10.0	77.0	0	15.0	0	92.0	0	1.0	2.0	5.0	7.0	0	0	+++
..	..	..	..	12	25	Ser. Fib.	7.7	0.8	0	0	26.0	0	26.0	0	46.0	6.0	10.0	16.0	2.0	10.0	+++
..	..	..	..	18	40	Ser. Fib.	7.8	15.5	4.0	0	0	0	4.0	12.0	62.0	14.0	6.0	20.0	0	2.0	++++
14	21	0	16	18	..	Ser. Sang.	7.8	14.3	31.5	5.0	4.5	0	41.0	0	31.5	7.0	16.0	23.0	4.0	0.5	++++
15	26	VII	9	27	10	Ser. Fib.	7.8	4.5	2.0	0	0	0	2.0	71.0	21.0	3.0	1.0	4.0	0	0	+
..	..	..	..	37	10	Ser. Fib.	7.8	2.9	0	0	0	0	0	70.0	20.0	7.0	3.0	10.0	0	0	+
..	..	..	..	43	10	Ser. Fib.	7.8	3.7	0	0	0	0	0	57.0	36.0	6.0	1.0	7.0	0	0	+
						Patients treated with specific sera.															
16	24	I	4	4	6	Ser. Sang.	7.8	.....	81.0	0	1.0	6.0	88.0	0	1.0	5.0	5.0	10.0	0	0	++
17	22	II	4	5	30	Ser. Sang.	...	39.6	48.0	0	2.0	1.0	51.0	1.0	3.0	5.0	31.0	36.0	8.0	1.0	++++
4	21	I	5	6	2	Ser. Sang.	...	...	70.0	2.5	1.0	0.5	74.0	0	0	1.0	22.5	23.5	2.0	0.5	++++
18	27	I	4	7	20	Ser. Sang.	8.0	4.3	50.5	0.5	5.5	0	56.5	0	14.0	16.5	11.5	28.0	0.5	1.0	+++
19	42	I	18	17	50	Ser. Sang.	8.0	0.4	16.0	44.0	8.0	0	68.0	12.0	8.0	0	4.0	4.0	0	8.0	++
20	19	I	15	17	1	Sang.	...	...	44.0	0	4.0	0	48.0	0	12.0	0	14.0	14.0	1.0	17.0	++++

tained numerous large copper-colored granules. They were encountered, in significant numbers (12% or more), in the fluids from 3 cases. These were all sterile effusions obtained after the middle of the 3d week of the disease, the highest percentage (71%) being noted on the 27th day and later in Case 15.

Little is known about the function of eosinophils. Bunting[40] considers the breakdown products of lymphocytes specifically chemotactic for eosinophils, thus explaining their occurrence in the lymph nodes in Hodgkin's disease. Schwartz,[29] on the basis of the association of eosinophilia and protein sensitiveness, suggests that the split products of protein absorption, such as occur in pleural fluids, are eosinotactic. The data for cases of pleural eosinophilia associated with pneumonia[29–32] as well as the experimental evidence

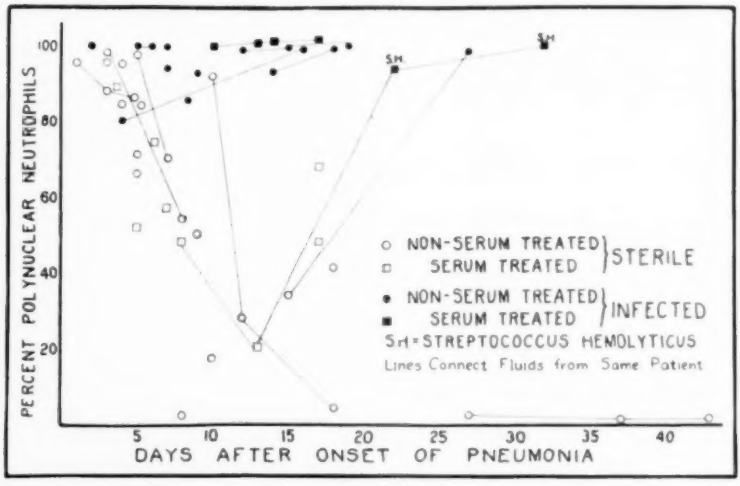

FIG. 1.—Relation of polymorphonuclear neutrophils in pneumonic pleural fluids to the course of the disease.

of Cunningham[41] indicate that eosinophilia appears only in fluids of relatively long standing. This corresponds with the present findings. There was no particular correlation of the high eosinophil counts with the finding of numerous erythrocytes, as suggested by Cunningham[41] or with high percentage of lymphocytes as indicated by Bunting.[40] Only moderate blood eosinophilia has been found in the reported cases of pleural eosinophilia,[30] and this was also the experience in Case 15 as indicated in Table 2.

TABLE 2.—EOSINOPHIL PERCENTAGES IN CASE 15.

	Per cent eosinophils.	
Day of disease.	Pleural fluid.	Blood.
27	71	10
37	70	12
43	57	4

Monocytes as they appeared in the fluids studied were, for the most part, identical with those in the blood. The cytoplasm tended to form sharp pointed pseudopods and contained salmon-pink granules and fine mitochondria. The nucleus was round or indented. Atypical forms were observed, however, in which the cytoplasm was edematous and billowed out widely around the nucleus. These forms probably represent early degeneration since similar forms were observed in the blood and novocain mixtures previously mentioned.

Macrophages (*Clasmatocytes*). These cells which were described in detail by Sabin[42] were large cells, each with single round nucleus containing nucleoli and with cytoplasm containing ingested erythrocytes, other particulate matter and few or numerous vacuoles of varying color. These cells often occurred in clumps of 4 or more, usually associated with monocytes or other cells.

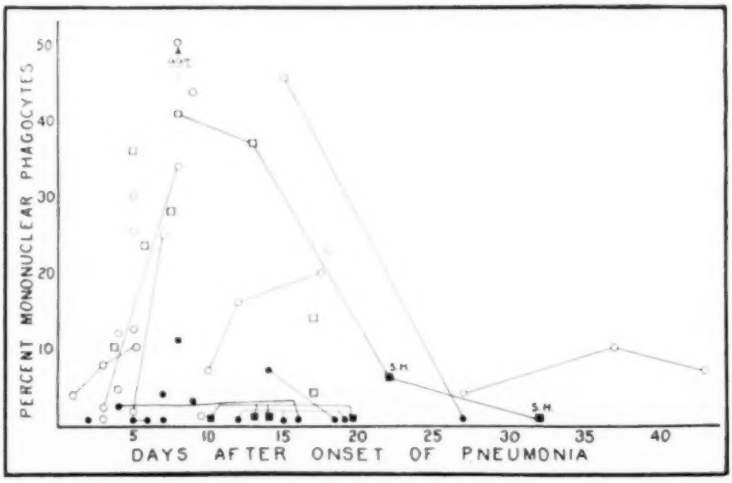

FIG. 2.—Relation of mononuclear phagocytes in pneumonic pleural fluids to the course of the disease.

Forkner[43] and other authors consider that, under stimulation, monocytes can become macrophages. In this study, the monocytes were not infrequently observed to become filled with a large number of vacuoles, making them morphologically indistinguishable from macrophages. These 2 types of closely related cells are, for convenience, grouped together as *mononuclear phagocytes*. As will be seen from Fig. 2, these cells behaved in the reverse manner to the polymorphonuclear neutrophils. Early in the disease they were few or absent in all cases. In sterile fluids the percentage rose rapidly. In fluids infected early they failed to appear, and in those later becoming infected they rapidly disappeared.

The rôle of these phagocytic cells is not entirely clear. Ylppö[27] attributes to them the fact that the most serous effusions fail to become purulent. Petzetakis[44] found that serous effusions accompanying simple bronchitis in children have a high percentage of these cells early in the disease. This may account for the absence of empyema in such cases, the mononuclear phagocytes acting as a protective barrier. Gay and his coworkers[1–5] showed that the clasmatocyte serves to protect against experimental streptococcic infections and, possibly, also against pneumococcic infections[6] in the pleura of rabbits. In the present series only 3 of the 20 cases with a total of over 10% of combined monocytes and macrophages ever became infected.

Lymphocytes. These were mostly small cells resembling the small lymphocytes of the blood, although a few cells of intermediate size were usually present. Significant numbers (over 10%) were observed in 9 cases, one of which had infected fluid at the time and 2 others in which the fluid later became infected. With one exception (Case 22), more than 10% lymphocytes were observed late in the disease and after the crisis. Their appearance followed several days after the rise in mononuclear phagocytes.

Some defensive rôle is generally assigned to lymphocytes in certain infectious diseases, particularly in tuberculosis, where it is felt that an increase in these cells at the expense of the monocytes indicates an increase in the patient's resistance. Reich and Reich[45] found, during convalescence from severe infections, a shift to the left of the lymphocytic hemogram, similar to that which is commonly found with the polymorphonuclear cells during other infections. In the present series of cases there appears to be some relation between the lymphocytes and the resolution of the inflammatory process in the lungs, the appearance of these cells following, in sequence, after the height of the increase in the polymorphonuclear and in mononuclear phagocytic cells. They could not be considered entirely protective inasmuch as one-third of the fluids with over 10% lymphocytes became infected.

Mesothelial Cells. These were very large cells containing 1 or 2 nuclei characterized by a well-defined nuclear membrane and nucleoli. The cytoplasm was usually unstained and contained many small unstained refractile globules. Some contained, in addition, a number of red vacuoles of varying size (Plate I). Cunningham[41] described similar vacuoles in mesothelial cells from animals with marked peritoneal irritation and considered them a sign of degeneration. This author and Sabin[42] consider these mesothelial cells to be fully differentiated cells which line the serous surfaces but have no phagocytic properties. They were seen, in the present series, fairly constantly as small numbers of desquamated cells. No transitional forms were noted and none of the cells were seen to exhibit phagocytosis.

In addition to the cells described above, occasional *myelocytes*, *foreign body giant cells* and *polymorphonuclear basophils* were noted (Table 1, footnote). The latter occurred in Case 15 in association with the increase in eosinophils. A similar basophilia was noted by Bayne-Jones in his cases of pleural eosinophilia.[30]

Summary. A supravital technique was used to study the cytology of 53 pleural fluids from 32 patients with pneumococcus lobar pneumonia. The cell types encountered are described. Their occurrence and frequency are correlated with the outcome of the effusion and the course of the pneumonia.

The cellular content of the infected fluids consisted almost exclusively of polymorphonuclear neutrophils in various stages of degeneration. In uninfected fluids the predominating cells, in the beginning, were active polymorphonuclear neutrophils, but these decreased in number during the first week at which time monocytes and macrophages appeared in the fluid. Later in the disease, after crisis had taken place, lymphocytes began to appear in these sterile fluids.

Moderate to marked eosinophilia was noted in 3 cases. This occurred during the 3d week, or later, after the onset of the pneumonia.

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THE OCCURRENCE OF MYELOCYTES IN THE PERIPHERAL BLOOD IN LOBAR PNEUMONIA.

By D. J. Stephens, M.D.,

INSTRUCTOR IN MEDICINE, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY; ASSISTANT PHYSICIAN, STRONG MEMORIAL HOSPITAL, ROCHESTER, N. Y.

(From the Department of Medicine, The University of Rochester School of Medicine and Dentistry and the Medical Service of the Strong Memorial Hospital and the Rochester Municipal Hospital.)

The voluminous literature on the blood findings in pneumonia contains but few references to the occurrence of myelocytes in the peripheral blood. In 1898 Turk[1] found that "mononuclear neutrophilic leukocytes" occurred in small numbers during the acute stage of the disease, in larger numbers at the time of the crisis and immediately thereafter, and similar observations have been made by Gaitskell,[2] Schindler[3] and Hittmaier.[4] In 26 of 36 cases of lobar pneumonia reported by these 4 authors, significant numbers of myelocytes were noted in the peripheral blood; the maximum myelocyte response occurred during the week following the crisis and varied in magnitude from 0.2 to 9.2% of the total leukocytes. In the available reports of others who have studied the blood in lobar pneumonia, myelocytes may have been included with stab forms under the heading of "immature neutrophils" but have not been mentioned specifically. In many of the patients described in the literature, hematologic observations have not been carried beyond the febrile period of the disease.

The investigation here reported was undertaken following the observation of a myelocytosis of considerable degree in the peripheral blood of a patient (R. P.) recovering from lobar pneumonia. The leukocyte response of 42 additional patients was studied in detail during the acute febrile and convalescent periods of the disease, using both fixed and supravitally stained preparations. In the majority, myelocytes were noted at some time during the period of observation. Especially noteworthy was the consistent appearance of a shower of myelocytes in the peripheral blood of convalescent patients during the immediate postfebrile period.

Method. Total white blood cell and differential counts were done daily during the febrile period. In patients who recovered, observations were continued at daily intervals for several days after the temperature became normal, somewhat less frequently during the latter period of convalescence. A total of 574 fixed and supravital preparations were studied. All of the differential counts (200 cells) were done by the author. In the fixed smears, using cover slips, Wright's stain, buffered dilution, Schilling's classification[4] was used. The supravital preparations were stained and studied by Sabin's[6] and Simpson's[7] method. In fixed smears, occasional mononuclear, granular cells were encountered, which were difficult to classify; such doubtful cells were uniformly classed as monocytes rather than as myelocytes or juveniles (late myelocytes). In the supravital preparations, the myelocytes observed were almost invariably the "C" type (Sabin). As a rule, when myelocytes were encountered in the peripheral blood, both fixed and supravital preparations were studied.

Except as to the myelocyte, our observations of the leukocytic response in lobar pneumonia were in accord with recent reports and may be briefly summarized. In fatal cases, as well as in those patients who recovered, the total white blood cell counts varied widely from case to case, and during the disease in the same patient. A valuable index of prognosis during the febrile period of the disease was to be found in the percentage of "stab" netrophils from day to day. A significant shift in the proportion of neutrophilic elements often preceded clinical manifestations of change by many hours. In 12 of 13 fatal cases there was a definite increase in single lobed neutrophils before death (Chart I). In patients who were to recover, the percentage of stab cells often began to fall hours or days before the decrease in temperature or clinical evidence of improvement, and usually dropped to an approximately normal level within a day or two after defervescence (Chart II). In the great majority of instances, spread of the pneumonic process or the development of a complication was accompanied by an increase or persistent elevation of the stab percentage (Chart III). Eosinophils were absent, or rarely present in extremely small numbers, throughout the febrile period in both fatal and recovered cases; they reappeared in small numbers at the time of crisis or lysis, and increased during convalescence. Convalescence eosinophilia was occasionally observed. The lymphocytes were uniformly decreased during the

febrile stage and gradually increased during the recovery period. A monocytosis at the time of defervescence or shortly thereafter,

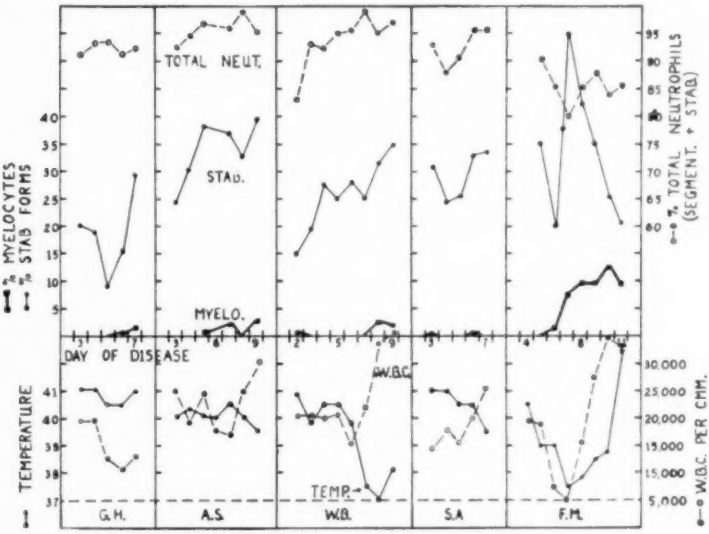

CHART I.—Neutrophilic leukocyte response of fatal cases.

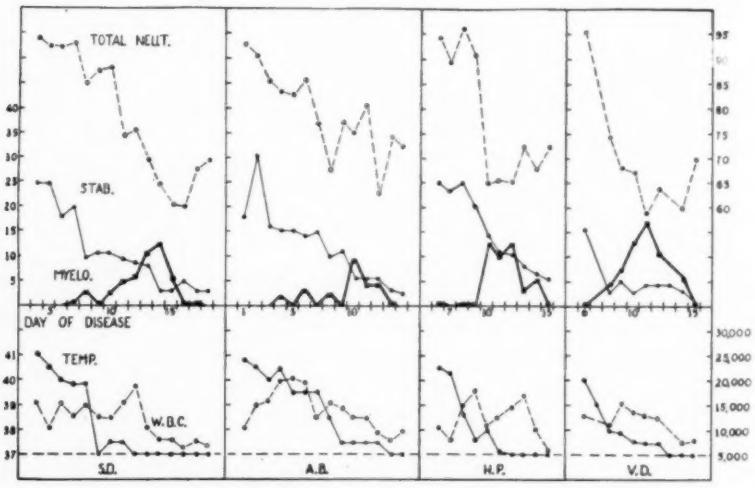

CHART II.—Neutrophilic leukocyte response of recovered patients.

recently emphasized by Hickling,[8] was observed in 13 of the 30 recovered patients. In 5 of these the monocytes comprised 10, 10, 10, 12 and 16% of the total leukocytes.

In the great majority of patients, small numbers of myelocytes were found in the peripheral blood during the early, febrile period of the illness. They were most frequently observed after the 3d or 4th day of the disease and were rarely present in excess of 1 or 2% of the total leukocytes. The degree and frequency of peripheral myelocytosis during the acute stage of the disease was approximately the same in those patients who were to recover as in those who died (Charts I and II).

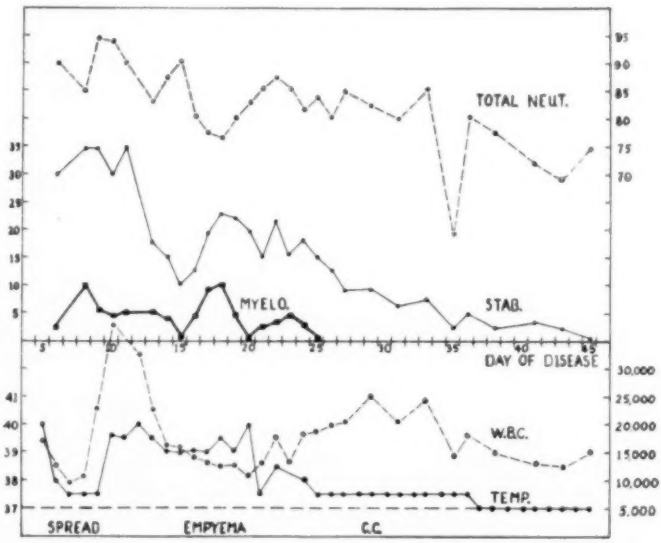

CHART III.—Neutrophilic leukocyte response in lobar pneumonia complicated by empyema.

In 12 of the 13 fatal cases, myelocytes were observed in the peripheral blood at some time during the period of observation. In 11 of these, the myelocyte increase was not striking, ranging from 1 to 3% of the total leukocytes. However, 1 patient (F. M.) exhibited a terminal increase in myelocytes to 12%. During the 5th and 6th day of the disease there was an apparent crisis, with drop in temperature, total white blood cells and stab neutrophils, coinciding with clinical evidence of improvement. On the 7th day there was an abrupt increase in the percentage of stab cells from 21 to 50% with the appearance of 7.5% of myelocytes (regenerative shift to the left of Schilling) although the temperature and total white blood cell count remained low. The next day there was evidence of spread of the pneumonic process. During the subsequent 3 days there was a progressive decrease in the percentage of stab cells, but a steady increase in myelocytes, total leukocytes, temperature and

clinical evidences of toxicity. The patient died on the 11th day with clinical and pathologic evidence of widespread pneumonia, empyema and pneumonococcic meningitis. Of the fatal cases, this was the only one of our small series who exhibited a definite "regenerative shift to the left," the prognostic significance of which has been stressed by Schilling. This was also the only patient in whom a terminal increase in the percentage of stab neutrophils was not observed. The temperature changes and the blood findings of this patient and of 4 other representative fatal cases are shown in Chart I. Eosinophils, basophils, lymphocytes and monocytes are omitted from the charts.

TABLE 1.—HEMOGRAM ON THE DAY OF MAXIMUM MYELOCYTE RESPONSE OF EACH OF 30 PATIENTS WHO RECOVERED FROM LOBAR PNEUMONIA.

Patient.	Day of disease.	Temperature.	Total W. B. C.	% Basophils.	% Eosinophils.	% **Myelocytes**	% **Juveniles**	% Stab forms	% Segmented forms	% Lymphocytes.	% Monocytes	% **Myelocytes supra-vital**	Remarks.
R. P.	12	37.2	11,850	0.5	1.0	**12.5**	**7.5**	11.5	42.5	23.0	1.0	**16.5**	Crisis 8 D.
V. D.	11	37.5	13,150	0.0	1.0	**16.0**	**1.0**	4.5	53.5	19.0	5.0	**15.0**	Crisis 6 D.
L. P.	10	39.6	43,600	0.0	2.5	**12.5**	**3.0**	14.0	59.5	7.0	1.5	**11.5**	Empyema.
G. B.	10	37.0	14,500	0.0	1.0	**10.0**	**4.0**	6.5	59.5	16.5	2.5	....	Crisis 8 D.
H. P.	10	38.0	11,200	0.0	0.5	**9.0**	**3.5**	14.0	53.0	18.0	1.0	**13.0**	Crisis 8 D.
S. D.	14	37.0	8,850	0.5	0.0	**9.5**	**2.5**	3.0	61.0	18.5	4.5	**10.0**	Crisis 9 D.
Ch. C.	14	37.5	13,600	0.5	3.0	**8.5**	**2.5**	4.5	56.0	17.5	2.5	**8.0**	Crisis 11 D.
C. C.	8	37.5	11,800	0.0	0.0	**8.5**	**1.5**	34.0	52.5	3.0	0.0	**11.0**	Empyema.
E. C.	7	38.2	19,800	0.0	0.0	**7.5**	**1.5**	8.0	67.0	12.5	3.5	**8.0**	Lysis 4–6 D.
G. C.	13	38.7	15,100	1.0	0.0	**8.0**	**1.0**	2.5	70.0	15.5	2.0	**9.0**	Empyema.
W. K.	10	37.5	10,700	0.0	1.0	**8.5**	**0.5**	4.5	48.0	34.0	3.0	**9.0**	Crisis 8 D.
L. R.	12	37.5	14,200	0.0	1.5	**8.5**	**0.0**	1.0	79.5	13.0	1.0	....	Crisis 7 D.
A. B.	10	37.6	13,300	0.0	0.0	**6.5**	**1.5**	6.5	69.0	6.5	8.5	**5.0**	Lysis 7–9 D.
A. T.	10	38.0	19,900	0.0	2.5	**7.0**	**1.0**	5.0	64.5	19.0	1.0	**7.0**	Lysis 7–10 D.
L. P.	11	37.5	20,800	0.5	0.5	**7.5**	**0.0**	1.5	72.5	14.0	3.5	**8.5**	Crisis 7 D.
W. K.	6	37.7	7,600	0.0	5.0	**6.0**	**0.5**	2.5	64.0	21.0	1.0	**5.5**	Crisis 3 D.
H. F.	10	38.0	14,000	0.0	1.0	**5.0**	**1.0**	6.0	73.0	11.5	2.5	**6.5**	Crisis 6 D.
P. G.	12	37.5	9,000	0.0	2.0	**5.5**	**0.0**	3.0	70.0	12.5	7.0	**6.5**	Lysis 7–10 D.
J. M.	?	39.2	26,000	0.0	0.5	**5.0**	**0.0**	8.0	77.0	4.0	4.5	....	Lysis.
V. K.	9	37.8	9,100	1.0	0.0	**4.5**	**0.5**	8.0	60.5	12.5	13.0	**6.0**	Lysis 5–7 D.
J. G.	15	37.5	11,250	1.0	2.0	**4.5**	**0.5**	4.0	68.5	14.5	5.0	**4.5**	Crisis 10 D.
G. F.	15	37.5	11,000	0.0	0.5	**4.5**	**0.0**	2.0	67.5	21.5	4.0	**5.0**	Crisis 11 D.
P. U.	10	37.3	7,300	0.5	1.0	**3.5**	**0.5**	2.0	66.0	26.0	0.5	....	Crisis 5 D.
P. W.	17	37.8	7,000	1.5	3.0	**2.5**	**1.0**	2.5	60.5	23.5	5.5	**3.0**	Lysis 3–6 D.
E. H.	7	37.5	8,400	0.0	4.5	**2.5**	**0.0**	1.5	61.5	25.5	3.5	**3.5**	Lysis 4–6 D.
W. R.	13	38.8	8,000	0.0	1.0	**2.0**	**0.5**	14.5	71.5	10.0	0.5	....	Lysis 8–13 D.
C. P.	8	37.3	5,250	0.5	0.5	**2.5**	**0.0**	1.0	77.5	16.0	2.0	**1.5**	Crisis 6 D.
N. T.	8	38.8	11,900	0.0	0.5	**1.5**	**0.5**	14.5	64.0	11.0	7.0	....	Crisis 4 D.
J. P.	5	37.5	7,350	0.0	6.0	**1.0**	**0.0**	7.0	58.0	20.0	7.0	....	Lysis 3–5 D.
F. R.	6	40.2	10,500	0.0	0.0	**0.0**	**1.0**	23.0	68.0	18.0	0.0	....	Lysis 8–14 D.

The most striking myelocyte response was observed in those patients who recovered. Although a mild myelocytosis was frequently observed during the febrile period, the maximum myelocytosis occurred after the acute manifestations of the disease had subsided. The temperature and hemogram on the day of the maximum myelocyte response in each instance are shown in Table 1. In two-thirds of the recovered patients, the myelocytes at their

maximum amounted to 5% or more of the total leukocytes; in almost one-third, to 10% or more; in 3 of them to more than 15%. The average myelocyte peak for the 30 cases was 7.5%. Of the 30 patients, 27 recovered without complications; in the majority of these the myelocyte peak was noted from 1 to 5 days after defervescence (Table 1). In 2 instances (N. T. and P. W.), the maximum myelocytosis occurred during serum sickness. In general, the myelocyte response was greater in those whose temperature fell by crisis than in those who recovered by lysis, but apparently it was not influenced by age, sex, or type of pneumococcus. Myelocytes usually appeared a day or two before the drop in temperature, attained a maximum 2 to 6 days later, and in most instances disappeared from the peripheral blood within a week. At the time of the maximum myelocyte response in uncomplicated cases, the temperature and percentage of stab neutrophils had fallen to an approximately normal level; frequently, however, there was still a definite elevation of the total leukocyte count. Chart II shows 4 typical neutrophilic responses.

In 3 cases complicated by empyema a marked increase in myelocytes occurred at about the same stage of the disease as in uncomplicated pneumonia, but persisted for a longer period of time. In patient C. C. (Chart III) a secondary myelocyte peak occurred at the height of the empyema and was accompanied by an increase in the percentage of stab neutrophils; the blood picture from the 15th to the 18th day was that of a progressive "regenerative shift to the left" and would ordinarily be interpreted as indicating a grave prognosis. If conclusions may be drawn from this small series of cases, the presence of immature myeloid elements in the peripheral blood in lobar pneumonia apparently has, at best, a very limited prognostic significance. One patient who died (F. M., Chart I) exhibited a definite "regenerative shift" on the 7th day, but the myelocyte increase occurred at about the same stage of the disease, in relation to the initial infection, as in recovered patients.

Small numbers of myelocytes in the circulating blood during the febrile period of the infectious diseases are not unusual; they have been observed in sepsis and in many infections (Schindler,[3] Schilling,[5] Naegeli[9] and others). In these cases myelocytes usually appear in the peripheral blood at a time when there is a marked increase in neutrophilic stab forms and is interpreted as being due to excessive stimulation of the bone marrow, resulting in the premature delivery of cells before they have reached the stab stage in their development. In lobar pneumonia, however, the maximum myelocyte response occurs at a time when the acute manifestations of the disease are subsiding; the temperature is normal or has approached normal and the commonly accepted evidences of bone marrow activity (total leukocyte count and, in particular, the percentage of stab

forms) are diminishing. Clinically, the myelocyte peak is accompanied by signs of resolution of the consolidated lung. Both clinical and hematologic conditions are quite different from those which prevail during the usually mild myelocytosis occurring during the acute stage of lobar pneumonia and other infections.

The stimulus responsible for the appearance of up to 15 or 20% of cells not normally present in the peripheral blood is not apparent. A postfebrile myelocytosis is not common to the infectious diseases; it has not been observed in bronchopneumonia or influenza, or in the postfebrile period of artificial hyperthermia. It may be significant that the maximum number of myelocytes was found in the peripheral blood at the time of resolution of pneumonic tissue. During this period nuclear material is liberated from the resolving exudate in considerable amount; the stimulating effect of certain nuclear derivatives on the bone marrow is well known. Although there is no direct evidence to support such an assumption, it is possible that the stimulating effect of nuclear material liberated at the time of resolution may be responsible for the observed myelocytosis, which apparently occurs to some degree in the majority of patients recovering from lobar pneumonia.

Summary. 1. In 43 unselected cases of lobar pneumonia, the white blood cell response was studied in detail, using both fixed and supravitally stained preparations.

2. In the majority of patients, small numbers of myelocytes were frequently found in the peripheral blood during the acute febrile period of the disease.

3. In patients who recovered, a consistent, and frequently striking, shower of myelocytes was observed in the peripheral blood during the period immediately following crisis and lysis.

4. It is suggested that the postfebrile myelocyte shower may be due to the stimulating effect of nuclear material liberated during resolution of the pneumonic exudate.

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EVANESCENT EFFECT OF INTRATIBIAL INJECTIONS OF BACILLUS WELCHII TOXIN IN RABBITS.*

By Leonard J. Goldwater, M.D.,
CLINICAL ASSISTANT VISITING PHYSICIAN, THIRD (N. Y. U.) MEDICAL DIVISION, BELLEVUE HOSPITAL; INSTRUCTOR IN MEDICINE, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY,

Joseph E. Connery, M.D.,
ASSOCIATE PROFESSOR OF CLINICAL PATHOLOGY, NEW YORK UNIVERSITY; VISITING PHYSICIAN TO BELLEVUE HOSPITAL,

AND

Harry Heimann, M.D.,
NEW YORK, N. Y.

(From the Department of Medicine, University and Bellevue Hospital Medical College, New York University.)

In 1929 Torrey and Kahn,[1] by intratibial injection of 0.5 cc. of hemolysin free B. welchii toxin, produced in rabbits an anemia resembling, hematologically, pernicious anemia in man. Beard, Clark and Moses[2] confirmed the findings of Torrey and Kahn. Furthermore, these observers were able to relieve the anemia by the administration of suitable doses of a known potent extract of liver.

The purposes of our study were (*a*) to attempt to confirm the results of the above investigators, and (*b*) to apply their technique to the biologic assay of the potency of certain specific anti-anemic substances.

Materials and Methods. The animals used in the study were healthy adult rabbits of approximately the same age and weight. They were housed in individual cages and fed what was considered an adequate diet. The toxin was an hemolysin-free B. welchii toxin.† Blood was obtained from the marginal ear vein for numerical estimations, morphologic studies and reticulocyte percentage determinations. Hemoglobin estimations were made by the Klett-Newcomer method. Estimations were made at intervals short enough to permit detection of significant changes. The hematologic determinations were made by the same person throughout the period of study.

After a control period of 12 days 3 rabbits received a single injection of 0.5 cc. and 2 rabbits were given 0.75 cc. of toxin, respectively. The toxin was injected intratibially according to the technique of Kahn and Torrey.[1] Two additional rabbits were followed

* This is No. 1 of a series of studies on the assay of biologic materials used in the treatment of the macrocytic hyperchromic anemias.

† This toxin was supplied by Drs. Kahn and Torrey of the Cornell Medical College.

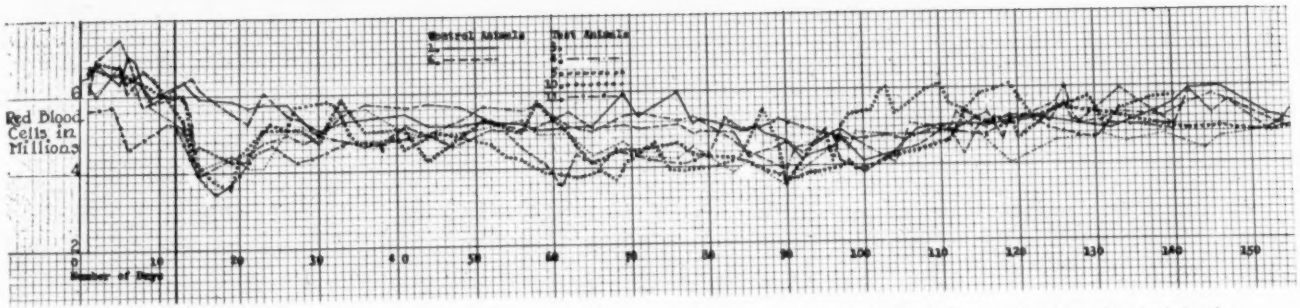

CHART I.—Total red blood cell counts in the rabbits. The heavy vertical line on the 12th day indicates the day of toxin injection.

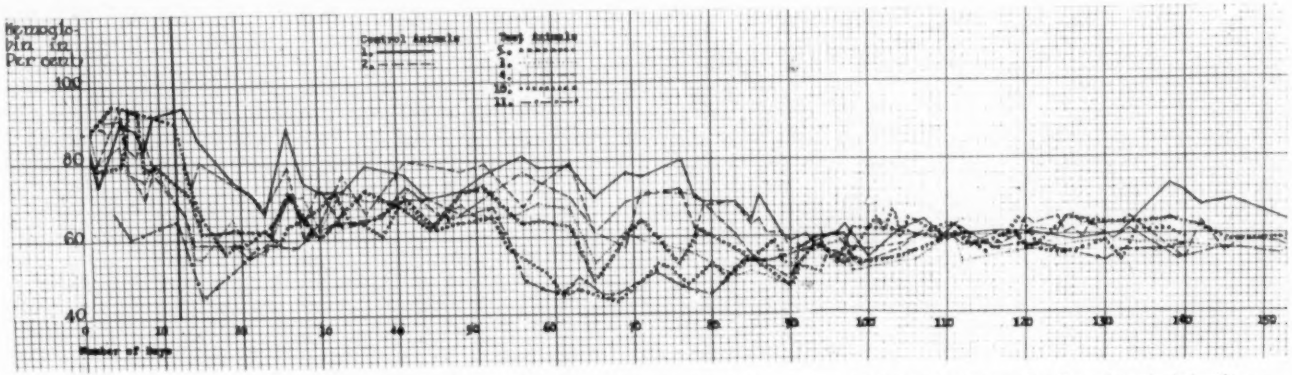

CHART II.—Hemoglobin determinations in the rabbits. The heavy vertical line on the 12th day indicates the day of toxin injection.

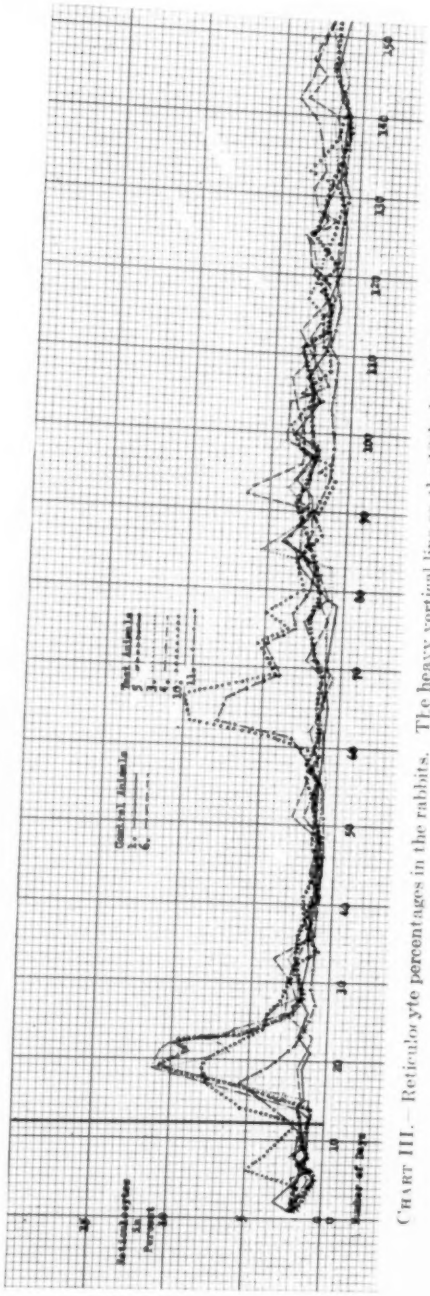

CHART III.—Reticulocyte percentages in the rabbits. The heavy vertical line on the 12th day indicates day of toxin injection.

as controls. The 7 rabbits were studied for 154 to 156 days. Since all the animals receiving toxin responded in practically the same manner regardless of the dosage of toxin, they were considered as a single group.

Results. *Red Blood Cells and Hemoglobin.* The red cells of the test animals showed a beginning fall on the day following injection of toxin (Chart I). The fall was maximal between the 5th and 7th days. No such fall was observed in the control animals. Following the initial fall there began a slow, steady rise of the curves, so that by the 110th day the curves of the test and control animals were at approximately the same level, and continued so thereafter.

The hemoglobin determinations (Chart II) closely followed those of the red blood cells.

Reticulocytes (Chart III). The reticulocyte curves rose as the total red blood cell counts fell; and again fell as the red blood cell counts rose. In the case of the 2 animals which were given 0.75 cc. of the toxin (Rabbits 10 and 11), rises were noted in the reticulocyte curves between the 60th and 70th days. The explanation for this finding is obscure. Interesting to note is the fact that a fall in the hemoglobin curves, also unexplained, occurred synchronously with the reticulocyte rises in the same 2 animals.

White Blood Cells. No significant changes in the curves of the white blood cells of the test or control animals were noted.

Morphologic Alterations in the Red Blood Cells. At no time during the experiment did the red blood cells of the test animals present the qualitative changes usually associated with pernicious anemia in man.

Color Index. The color index never rose to unity or above.

Summary and Conclusions. In our search to find a suitable method for assaying the potency of substances effective in the treatment of the macrocytic hyperchromic anemias we attempted to induce an anemia in rabbits by a single intratibial injection of hemolysin-free B. welchii toxin. Since the changes in the blood of the test animals were quite evanescent and since the blood picture of the test animals rapidly returned to a condition similar to that seen in the control animals, this method was deemed unsatisfactory for our purposes.*

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2. Beard, S. D., Clark, G. W., and Moses, M. J.: Proc. Soc. Exp. Biol. and Med., **26**, 13, 1928.

* From a personal communication from Dr. G. W. Clark we quote: "In a period from February 7, 1929, to March 4, 1931, 100 rabbits received intramarrow injections (tibia) using 37 different strains of B. welchii toxin prepared by the Anaërobic Department of the Lederle Laboratories and three welchii toxins prepared in one of the New York hospitals. None of these toxins has given the results reported earlier by Beard, Clark and Moses."

LACK OF EFFECT OF LIVER TREATMENT ON THE CIRCULATING RETICULOCYTES IN THE PIGEON.

By Harry Heimann, M.D.,

Joseph E. Connery, M.D.,

ASSOCIATE PROFESSOR OF CLINICAL PATHOLOGY, NEW YORK UNIVERSITY; VISITING PHYSICIAN TO BELLEVUE HOSPITAL,

AND

Leonard J. Goldwater, M.D.,

CLINICAL ASSISTANT VISITING PHYSICIAN, THIRD (N. Y. U.) MEDICAL DIVISION, BELLEVUE HOSPITAL; INSTRUCTOR IN MEDICINE, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY,
NEW YORK, N. Y.

(From the Department of Medicine, University and Bellevue Hospital Medical College, New York University.)

According to Vaughan, Muller and Zetzel,[1] and Vaughan, Muller and Minot,[2] the feeding of an inadequate diet to pigeons results in a decrease in the percentage of the circulating reticulocytes. Further, the addition to the diets of materials effective in relieving the macrocytic hyperchromic anemias of man produces an increase of the percentage of the circulating reticulocytes of test animals. For these reasons, and because of the fact that the bone marrow of pigeons is megaloblastic, it seemed to Vaughan and her collaborators that pigeons might be used in the biologic assay of the potency of materials used in the treatment of anemia associated with a megaloblastic type of bone marrow (pernicious anemia).

The purposes of this study were (*a*) to test the validity of the above hypotheses and (*b*) to apply this technique to the biologic assay of the potency of materials used in the treatment of the macrocytic hyperchromic anemias.

Materials and Methods. Healthy adult pigeons were obtained from the open market and were housed in individual cages in a well ventilated room. Food and water were supplied in abundance and were changed daily. The cages were cleaned frequently without changing their relative positions in the room. Two diets were used: "complete" and "incomplete." The "complete" diet consisted of equal parts of flint corn, vetch, and Canada peas, and canary seed with abundant amounts of grit and lettuce. The "incomplete" diet consisted of the above without the canary seed, grit and lettuce. Three known potent commercial preparations of liver "fraction G" were used: (*a*) powdered extract, prepared from mammalian liver for oral administration,* (*b*) a solution of the same powdered extract for parenteral administration,* and (*c*) an aqueous solution pre-

* The mammalian liver fractions were supplied by the Lederle Laboratories.

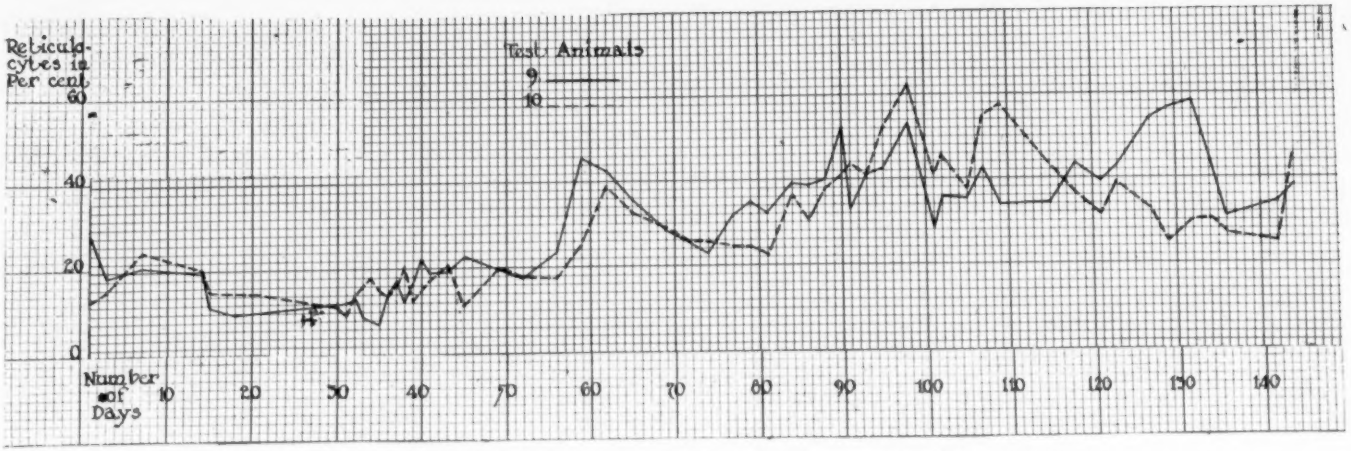
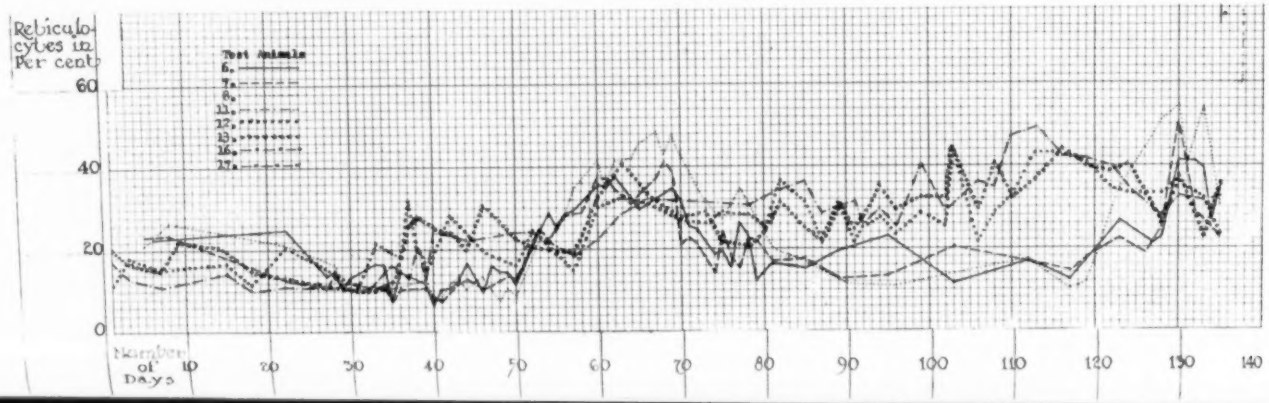


CHART I.—Reticulocyte percentages of pigeons on complete diet.



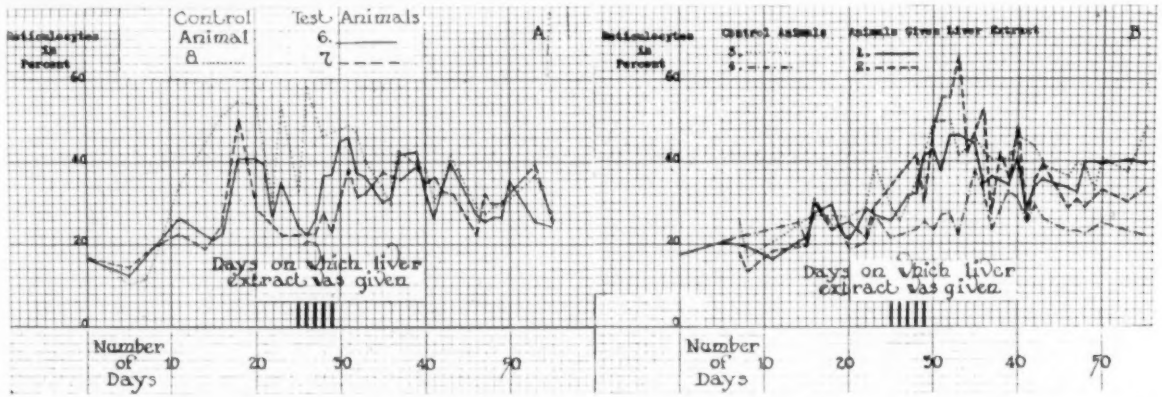


CHART III.—Reticulocyte percentages in pigeons which were given mammalian liver extract by mouth for five successive days. *A*, pigeons on "complete" diet; *B*, pigeons on "incomplete" diet.

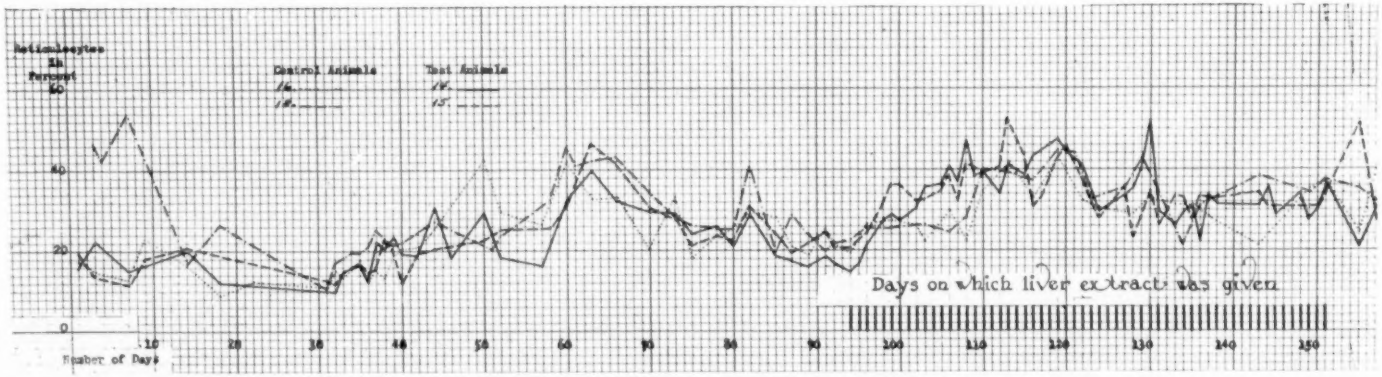


CHART IV.—Reticulocyte percentages in pigeons on the incomplete diet which were given mammalian liver extract by mouth for 57 successive days.

pared from the liver of the cod.* The powdered extract was used in solution of such concentration that 2 cc. contained the material derived from 4 gm. of raw liver. The powdered extract was given by stomach tube as was the fish liver extract. The solution for parenteral administration was of such strength that 5 cc. contained the material derived from 100 gm. of raw liver. All liver extracts were administered at the same time of day.

Blood for all examinations was obtained from the wing veins of the pigeons. Bleeding was easily controlled. Reticulocytes were counted according to Vaughan's modification[1] of Cunningham's method.[3] All the red blood cells showing any reticulum in the cytoplasm were included as reticulocytes.† Hemoglobin estimations were made by the Klett-Newcomer method. Hematologic determinations were made frequently on samples of blood drawn at the same hour of each day. The birds were weighed about 3 times each week.

Results and Discussion. *Reticulocytes in Pigeons Receiving the "Complete" Diet.* Two pigeons were kept on the "complete" diet for a total of 144 days. As may be seen from inspection of Chart I, the reticulocytes showed considerable variations from week to week and even from day to day. The variations between two successive counts were often as great as 20% of the total red blood cells.

Reticulocytes in Pigeons Receiving the "Incomplete" Diet. Eight birds were kept on the "incomplete" diet for 135 days. From inspection of Chart II it can be seen that there is a downward trend of the circulating reticulocytes ending on about the 26th day, then an upward trend to the 65th day, followed by a second fall reaching its lowest level on the 74th day. Because of the undulatory character of the curves no prediction could be made as to the expected curve in any one case. By comparison of Charts I and II it can be seen that the individual variations of the reticulocyte percentages of the birds on both diets, "complete" and "incomplete," showed striking similarity.

Reticulocytes in Pigeons Receiving Liver Extract. From inspection of Chart III (*A* and *B*), it is apparent that the daily oral administration of potent liver extract (the material derived from 4 gm. of raw liver) for a period of 5 days produced no significant changes (*a*) in the type of the curves or (*b*) in the trends. This observation applies to pigeons receiving the "complete" as well as those receiving the "incomplete" diet. Because of the possibility that the test period of 5 days was not sufficiently long to permit of significant changes to occur, 2 birds which had been receiving the "incomplete"

* The fish liver extract was supplied by the White Laboratories.

† Some of the reticulocytes seemed to warrant separate enumeration because (1) of the density and amount of reticular material, (2) the fact that the reticulum encircled the nucleus, completely in many cases, and (3) the ease with which these cells could be identified. Irrespective of the dietary the number of these forms varied between 1% and 7% of the total red blood cells.

diet were fed potent mammalian liver extract (the material derived from 4 gm. of raw liver) daily for a period of 57 days (Chart IV). Here, again, it may be observed that the feeding of potent liver extract in large daily doses over a long period of time was without effect on the circulating reticulocytes in the blood of the test animals. In order to obviate the possibility of the failure of absorption of anti-anemic substances from the gastro-intestinal tract of the test birds[4] being responsible for the lack of effect on the circulating reticulocytes, 2 pigeons receiving the "incomplete" diet were each given 1 cc. (containing the material derived from 20 gm. of raw liver) of a solution of liver extract by injection into the breast muscles. This experiment yielded negative results. As a further observation, 2 pigeons, also receiving the "incomplete" diet, were fed large daily doses of potent fish liver extract for 15 days, also without effect on the circulating reticulocytes.

Conclusions. From these experiments the following conclusions seem warranted:

1. The percentage of the circulating reticulocytes in the blood of the pigeon is subject to wide fluctuations.

2. The various test substances used in this study, including the "incomplete" diet, had no significant effect upon the percentage of the circulating reticulocytes in the pigeon.

3. In our hands this technique does not lend itself to the biologic assay of the potency of materials used in the macrocytic hyperchromic anemias.

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SPONTANEOUS RUPTURE OF THE HEART SIMULATING SURGICAL ABDOMINAL DISEASE.*

By Harry A. Salzmann,

ASSISTANT, SURGICAL SERVICE, NO. 2, MT. SINAI HOSPITAL; ASSISTANT, SURGICAL SERVICE OF DR. F. A. MC CARTHY, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

(From the Staedtische Krankenanstalten, pathological institute, Professor Loeschke, director, Mannheim, Germany.)

Following infarction of the myocardium, the patient may die, healing by scar formation may take place, or less frequently spontaneous rupture of the heart may result. That such grave changes

* Read before the Southeastern Branch of the Philadelphia County Medical Society, February 1, 1934.

in the heart muscle, even where rupture occurs, may assume the clinical picture of an abdominal catastrophe is not generally appreciated.

Four cases of spontaneous rupture of the heart and one of rupture of an aortic aneurysm, all admitted to the surgical division of the hospital because of suspected acute abdominal disease, have led us to consider this rather rare condition more closely. The fact that abdominal pain not infrequently is the only important symptom in disease of the cardiovascular system and may lead to confusion with lesions requiring operative treatment makes this condition of particular interest to the clinician.

In 5000 postmortem protocols, I was able to find only 6 cases of proven spontaneous cardiac rupture and 1 of rupture of an aneurysm of the aorta causing tamponade of the heart.

One may realize the rareness of this condition from the following: Krumbhaar and Crowell found only 7 cases in 16,000 autopsy reports; Romeick (Munich) 7 in 13,000 protocols, and in 8000 autopsies at Leipzig only 9 cases of spontaneous rupture of the heart were found.

A report of our own cases with a brief abstract of the clinical and postmortem findings follows:

Case 1.—W. W. (946/1931), aged 51 years, male, carpenter, had vague abdominal pains for the past 3 or 4 years; and recently, attacks of weakness and dizziness. Five days before admission he was suddenly seized with severe pains in the upper abdomen, vomited and was treated for suspected gall-bladder disease. He then attempted to get up out of bed but suddenly collapsed and was immediately brought into the hospital in a condition of shock.

Physical examination revealed an emaciated male, pulseless, and complaining of excruciating pains in the upper abdomen. The mucous membranes were pale; the respiratory excursions were rapid and shallow. The cardiac border was somewhat enlarged to the left, heart tones were weak and the heart action was irregular and rapid, no murmurs nor pericardial friction rub were heard; the radial pulse could not be felt; the patient vomited continuously. The abdomen was not distended, there was circumscribed tenderness on pressure in the epigastrium; the abdomen was otherwise negative except for slightly increased tension in the epigastrium.

The first thought was that we were dealing with a covered perforated ulcer. Because of the poor general condition of the patient operation was delayed. Following supportive treatment the pulse improved after several hours. Fluoroscopic examination of the abdomen gave a negative result. The Roentgen ray shadow of the heart showed a marked enlargement and a mitral configuration. Thirteen days after the onset of the present illness the patient had an anginoid attack, he again became pulseless and the temperature rose to 103.1°; at this time he again complained of severe pains in the upper abdomen. Two days after this attack the patient's condition became somewhat better and he was transferred to the medical division with the diagnosis of coronary sclerosis and thrombosis.

A Roentgen ray taken 16 days after the onset of the present illness gave the following findings: indefinite cardiac silhouette with considerable widening toward the left, and with some widening toward the right. The configuration of the cardiac outline is flabby. Pulsation could be seen only in the region of the large vessels. The cardiac border pulsated very un-

equally. The cardiac diameter was 17.6 cm. Electrocardiograph diagnosis on the same date: perpetual arrhythmia and tachycardia, severe heart muscle damage. Cardiac infarct?

The patient suffered several aginoid attacks and finally he became comatose; the coma was attributed to uremia. U.N. was 225. His coma became more pronounced until he died 27 days after the onset of the present illness.

Autopsy (167/1931): Sclerotic closure of the posterior coronary artery. Cardiac muscle infarct with perforation on the posterior wall of the left ventricle and large hemorrhage into the pericardial sac. Anemic infarcts of the kidneys. Radiating scar of ulcer in the fundus of the stomach.

CASE 2.—The patient was admitted to the surgical service with a history of severe kidney colic of several days' duration. He expired during the night of the same day.

Autopsy: Coronary sclerotic areas of myomalacia on the posterior wall of the left ventricle with perforation of the myocardium. Hemopericardium. Incomplete thrombosis of several of the arteries of the right kidney. Chronic pyelitis of the right kidney.

CASE 3.—The patient was admitted to the hospital for colicky pains suggestive of gall stones of 8 days' duration. He expired 15 minutes later.

Clinical diagnosis: Pancreatitis?

Autopsy: Atheromatous, and partially stenosing sclerosis of the coronary vessels. Perforation of the anterior wall of the left ventricle at the site of infarction, cardiac tamponade.

Lisa and Ring have recently reported an interesting case of occlusion of both coronary arteries with infarction and perforation of the left auricle. The patient was a 53-year-old white male, who gave a history of recurrent attacks of severe epigastric pain relieved by vomiting and alkalis. The symptoms lasted over a period of 4 years and the patient was subjected to operation on two different occasions. At first an appendectomy was performed and an apparently normal appendix was removed, with no relief of symptoms. A year later a diagnosis of duodenal ulcer was made and the patient was at first treated by Sippy diet with no relief. An electrocardiogram showed abnormal inversion of the *T* wave in Leads I and II and a suggestion of a coronary *T* wave in Lead III. In spite of the evidence of coronary lesions the patient's abdominal symptoms became so severe that a gastroenterostomy was performed, although no ulcer was found at operation. After a stormy convalescence he left the hospital. The symptoms became more severe and a year before his final illness he began to have precordial pain and showed clinical signs of decompensation such as cyanosis, edema, pleural effusion, and gallop rhythm. The patient finally died 4 years after the onset of symptoms and autopsy revealed occlusion and sclerosis of both coronaries with infarction and perforation of the left auricle just above the base of the posterior mitral cusp.

CASE 4.—J. B. (3337/1926), a 50-year-old laborer, claims that he was never seriously ill until present illness. On the day of admission he was seized with excruciating pains in the upper abdomen and was sent into the hospital for operation with a diagnosis of cholelithiasis or pancreatitis.

Physical examination revealed a well-developed male; with irregular heart action, and small, rapid pulse. The abdomen was slightly distended

and diffusely tender, especially in the upper abdomen to the right of the mid-line. After the administration of cardiac stimulants immediate operation was undertaken. Upon opening the abdomen the gall bladder appeared macroscopically diseased and was removed. During the operation cardiac stimulants had to be administered repeatedly; near the end of the operation the patient improved. The wound healed *per primam* and the patient felt very well. Histologic examination of the gall bladder revealed no inflammatory changes. On the 12th day following operation while the patient's condition was very good he suddenly developed air hunger, became very weak and expired almost immediately.

Clinical diagnosis: Cholecystitis; postoperative pulmonary embolism.

Autopsy: Luetic aortitis with two aneurysms; rupture of the intrapericardial aneurysm situated in the beginning portion of the aorta with hemopericardium and cardiac tamponade.

CASE 5.—The patient had severe upper abdominal pains of 2 days' duration; sudden death 2 days following admission.

Autopsy: Cardiac rupture in the middle of a myomalacious focus of the anterior wall of the left ventricle. Obliteration of the left coronary artery. Dilatation of both ventricles. Advanced generalized arteriosclerosis.

CASES 6 and 7, developed cardiac rupture unaccompanied by abdominal symptoms.

CASE 6, *Autopsy:* Perforated cardiac aneurysm. Coronary sclerosis.

CASE 7.—A. L., 59-year-old male, was brought into the hospital dead after having suddenly collapsed and it was supposed that death was due to an apoplectic stroke.

Autopsy: Perforation of the left ventricle. Coronary sclerosis.

The following tables present a short review of our own cases and Krumbhaar and Crowell's cases.* Table 1 shows the cases arranged according to the underlying disease. As many of the series in the first column were from old reports they undoubtedly understate the frequency of infarct formation (see high incidence of "fatty heart").

TABLE 1.—ETIOLOGY.

	Krumbhaar and Crowell series.	Author's series.	Total.	Per cent.
Coronary sclerosis with occlusion and infarct formation	145	93	238	32.9
Coronary disease combined with various myocardial lesions	113	5	118	16.3
Cause undetermined; coronary arteries apparently normal	11	...	11	1.6
Coronary arteries not described	68	4	72	10.0
Heart apparently normal	5	...	5	0.7
Fatty heart	186	1	187	25.9
Myomalacia	42	1	43	6.0
Aneurysms	32	2	34	4.5
Malignant endocarditis	...	1	1	0.1
Lues	5	1	6	0.8
Tuberculosis	1	...	1	0.1
Abscess following septicemia	...	6	6	0.8
Echinococcus cyst	2	...	2	0.2
Tumor metastases	1	...	1	0.1
Total	611	114	725	100.0

* Davenport, A. B. (AM. J. MED. SCI., **176**, 62, 1928) reports 57 cases gathered from the literature, but since the author's references were not published, we are unable to include his material in this analysis.

Table 2 gives a summary of the position of the perforation. According to this the left ventricle is most frequently the site of rupture.

TABLE 2.—SITE OF THE RUPTURED AREA.

	Krumbhaar and Crowell series.	Author's series.	Total.	Per cent.
Right auricle	35	1	36	5.2
Left auricle	12	2	14	2.0
Right ventricle	63	10	73	10.5
Left ventricle	493	61	554	80.0
Mixed	15	1	16	2.3
Total	618	75	693	100.0

The area of predilection for the perforations in the left ventricle is the apical region, where the in arcts and the conditions arising from them are chiefly located and where, as Meyer states, the muscle layer of the heart wall is physiologically thinnest and also where, as Boettger claims, the pressure which the left ventricle has to withstand is supposed to be most forceful. Next in frequency to the apical region is the posterior wall of the left ventricle. The average age of the patients in whom we find a perforation of the auricle is less than in cases of ventricular perforation.

The actual mechanism of tear and rupture has never been fully explained. The chief factors at work in the infarct are softening, hemorrhage and the action of the adjacent active muscle surrounding the infarct. The internal opening of the perforation is usually placed at the base of a papillary muscle or at the junction of the septum and the outer heart wall; both points which are subjected to the stress of divergent action of the two main muscle masses. The presence of excessive mural fat, as was found in all of the cases reported by us, is responsible for the rapidity with which necrosis and the formation of a perforation takes place.

Table 3 gives a review of the age of the patients.

TABLE 3.—INCIDENCE ACCORDING TO AGE.

	Krumbhaar and Crowell series.	Author's series.	Total.	Per cent.
Over 85	30	3	33	4.7
80+	52	11	63	9.0
70–80	167	42	209	30.0
60–70	188	21	209	30.0
50–60	81	16	97	13.9
40–50	43	1	44	6.3
30–40	23	..	23	3.3
20–30	6	1	7	1.0
10–20	8	..	8	1.2
1–10	4	..	4	0.6
Total	602	95	697	100.0

The incidence of rupture in cardiac infarction has been estimated by Benson and Hunter and by others (*vide* Beresford and Earl) as about 6%. This is confirmed in the present review.

Among the 5000 autopsy protocols examined we were able to find a pathologic condition of the circulatory organs in 1224 cases in which the heart was affected 1142 times. Coronary sclerosis was found in 658 cases, 75 of which had progressed to occlusion with concomitant infarction; an indisputable spontaneous rupture of the heart could be shown only in 6 cases (8%). Of these, 5 were due to coronary sclerosis with occlusion and infarct formation; 1 to an aneurysm of the left ventricle.

Although the diagnosis of cardiac perforation was not made in any of the cases, nevertheless, only 1 of our 5 cases with abdominal symptoms was operated upon. The clinical phenomena in all of the cases were so severe that the patients had been sent in for immediate operation. However, it was deferred because the severity of the spontaneous abdominal pains was incompatible with the very moderate rigidity of the abdominal wall. The fact that the pain radiates upward under the sternum and possibly to the shoulder, especially toward the left shoulder and also the fact that tenderness to palpation in the upper abdomen is only moderate or absent, together with the history of previous attacks attributable to arteriosclerosis and/or myocardial changes (fainting spells, angina pectoris, dizziness, anxiety, etc.) all serve as points in the determination of the diagnosis.

In view of the etiology and the progressive myocardial damage we must regard surgical therapy as seemingly hopeless. The formation of connective tissue in cardiac muscle wounds is very light. For this reason the danger of a secondary hemorrhage due to a rupture of an insufficiently developed scar and the possibility of aneurysm formation is great, as has been pointed out by Klose.

The fact that myocardial infarction, even when severe enough to end in perforation of the heart, and even to a greater degree perforation of the aorta, and dissecting aneurysm of the aorta, may give rise to a symptom complex which may easily be confused with that of a pancreatic necrosis, cholelithiasis or nephrolithiasis is not sufficiently recognized. These conditions of the circulatory mechanism may lead to severe abdominal pain, frequently accompanied by vomiting and distention. If one finds these signs in older individuals and at the same time signs of severe myocardial degeneration are present (such as arrhythmias), one should always consider in such cases whether the pains are not the result of a cardiac condition. The question as to whether they are to be regarded as angina abdominalis caused by arteriosclerotic changes of the abdominal vessels, as described by Ortner, or whether they are to be regarded as cardiogastric pains due to distention of the pericardial sac, still remains open.

Levine, in his monograph on infarction, found that of 9 patients in whom rupture had occurred, 8 died within 2 weeks following the onset of infarction; of these 6 died between the 5th and 14th day. This, according to Levine, is the period when necrosis is most marked and the muscle is softest. The difficulty of differentiating between the symptoms of infarction and those of rupture make it impossible to calculate the length of survival after rupture has taken place.

A critical review of the cases reported in the literature as having lived for days or even weeks after rupture has occurred leads one to the conclusion that the symptoms of infarction have been confused with those of perforation. The mechanism of death in spontaneous rupture may theoretically be explained as based on the obstruction of the great veins by the raised intrapericardial pressure. In those cases where little blood is found in the pericardial sac the sudden death suggests ventricular fibrillation or some such disaster.

Summary. 1. Six cases of spontaneous rupture of the heart and 1 case of perforation of an aortic aneurysm are reported; 718 cases of spontaneous cardiac rupture gathered from the literature are reviewed.

2. Cardiac rupture most frequently occurs in an area of infarction 5 to 14 days following coronary occlusion. The most common site of the rupture is the left ventricle.

3. An important item for the clinician is that of differential diagnosis, because the condition frequently arises with severe symptoms attributable to diseased conditions of the abdominal organs. It may lead to con usion with pancreatitis, gall bladder and kidney colic, intestinal ileus, and other diseases of the abdominal viscera.

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ENLARGEMENT OF THE HEART DUE TO ABNORMAL GLYCOGEN STORAGE.

IN VON GIERKE'S DISEASE.*

BY WILLIAM ANTOPOL, M.D.,

JULIUS HEILBRUNN, M.D.,

AND

LESTER TUCHMAN, M.D.,

NEW YORK CITY, N. Y.

(From the Pediatric Service and the Laboratories of Christ Hospital, Jersey City, N. J., and the Laboratories of The Mount Sinai Hospital.)

GLYCOGENOSIS, or glycogen storage disease, was first described by von Gierke,[1] in 1929, as a pathologic entity under the name of "hepato-nephromegalia glycogenica." He gave a detailed pathologic description of 2 cases with massive glycogen deposits in the liver and kidneys. Schoenheimer[2] confirmed von Gierke's histologic findings by chemical analyses and attributed the disorder to a disturbance of the glycogen splitting mechanism.

Five necropsy reports of this disease are now on record, in 2 of which tremendous diffuse enlargement of the heart is described (Putschar[3] and Pompe[4]).

The present communication deals with a case which was clinically

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obscure, and which terminated with an intercurrent pneumonia. The markedly enlarged heart found at necropsy gave rise to the suspicion that the case was one of glycogenosis. Histopathologic and chemical studies proved the correctness of this opinion.

Case Abstracts.—R. K., a 4½-month white, German, male, was admitted to the Christ Hospital, Jersey City, N. J., on the service of Dr. Julius Heilbrunn on August 17, 1933. The mother had borne another child, now living and apparently normal. Two weeks prior to the birth of the patient, the mother showed a trace of sugar in the urine. From birth on the breathing of the infant was unusually rapid.

The weight at birth was 3250 gm.; 10 days later 3559 gm. The average weekly gain was 110 gm. except for the 4 weeks prior to admission, during which the child failed to gain.

Physical Examination. The general appearance is that of a fairly well-nourished infant, who does not appear acutely ill. The only positive findings are slightly enlarged cervical glands. Forty-eight hours after admission bronchial breathing and dullness over the right lower and middle lobes appear. The respirations are rapid and shallow, the facial expression anxious, and the features pinched. A diagnosis of pneumonia is made. Four days later, the left side of the chest shows similar findings.

Laboratory Findings: Hemoglobin, 75% (Sahli); white blood cells, 7800; polymorphonuclears, 28%; lymphocytes, 72%. Routine examination of the urine was negative. No examination for acetone.

Roentgen ray of chest 4 days after admission shows cardiac enlargement with no definite indications of pulmonary disease.

Roentgen ray of chest 1 day before death shows marked enlargement of the heart to the right and left with scattered areas of consolidation in the right upper lobe and a slight pleural exudate. The cardiac shadow obscures the underlying details in the left lung.

The infant did poorly in the hospital. Profuse diaphoresis, restlessness and cyanosis were the most prominent symptoms. During the 10 days in the hospital the weight declined 112 gm. The temperature was slightly elevated until the 10th day when it rose to 108° just before death.

Necropsy. We are indebted to Dr. F. H. Hemsath, pathologist, for the use of this material. Only a partial examination was permitted.

Heart. The heart is strikingly enlarged and weighs 85 gm. The pericardial cavity contains no excess of fluid. The pericardial surfaces are smooth and glistening. The presenting anterior surface is made up of both right and left ventricles (Fig. 1). The heart is in a state of contraction. The right auricular wall is moderately thickened, the right ventricle markedly so (10 to 16 mm.); the interventricular septal portion is 18 to 25 mm. thick. The left auricle is moderately hypertrophied and the endocardium is white, but smooth throughout. There is marked hypertrophy of the left ventricle (10 to 18 mm. thick). The very large and prominent papillary muscles almost completely fill the cavity of the contracted chamber. No changes are noted in any of the valves. The aorta is negative. The isthmus of the aorta is not narrowed.

Microscopic Examinations. The myocardium is composed of a network of cytoplasm of varying thickness (2 to 4 microns) (Fig. 2-*A*). In those places where the muscle is cut tangentially, the muscle cells appear in the form of hollow cylinders surrounded by delicately striated protoplasmic walls (Fig. 2-*B*.) The nuclei of the interstitial cells are for the most part compressed. The muscle nuclei, about 8 microns in diameter, are peripherally situated, have a definite nuclear membrane, and a moderate amount of chromatin material. Occasional atrophic muscle fibers as well as focal fibrotic areas are seen throughout the myocardium. An occasional small

collection of neutrophils and round cells is present. Perivascular fibrosis is prominent. The subendocardial connective tissue is widened.

The shrinkage is not as marked in the celloidin embedded tissue and the walls of the hollow cylinders appear thicker. Best's carmin stain shows the intracellular non-protoplasmic areas to be filled with rods and droplets which stain a deep brilliant red (Fig. 3). Similar droplets are noted in the interstitial tissue. These rods and droplets stain brown with iodin. Comparison of serial sections with both of these methods does not reveal any appreciable difference in the amount of stained substance, thus ruling out the presence of significant quantities of galactogen.[5]

The Sudan stain reveals a slight amount of neutral fat in the interstitial tissue. No neutral fat is present in the muscle fibers.

Bloodvessels. Microscopic Examination. Many of the bloodvessels are thickened, because of swelling of the muscle fibers. The muscular layer of the vessels, especially the larger veins, appears as a thin network of cytoplasm, and resembles the network described in the heart except that no striations are visible. The endothelium is swollen, and the elastica is prominent. The muscle fibers of the aorta and pulmonary artery present a similar picture. There is, however, an increase in the connective-tissue framework between the muscle fibers.

Best's carmin stain demonstrates glycogen droplets, which fill the vacuoles in the individual muscle fibers. This is very striking in longitudinal sections where the fusiform glycogen accumulations are seen in parallel rows. The endothelium is also filled with glycogen. Glycogen droplets are present within the lumen of many of the vessels.

Liver. The organ is enlarged. Its capsule is smooth. On cut section it has a grayish appearance. The lobular structure is not discernible.

Microscopic Examination. Hematoxylin-eosin stain reveals crowded cells with very few blood spaces between them (Fig. 4-*A*). The cell membrane is prominent. The cytoplasm of the liver cords contains both vacuoles and granules. The cells in the periportal areas are larger than the central cells, and are more frequently vacuolated. The nuclei are large, round, and eccentrically situated. Scattered throughout the parenchyma there are focal collections of neutrophils with an occasional round cell. Cellular structure is absent in these areas. The cells lining the smaller biliary channels are swollen and almost completely fill the lumen. There is no inflammatory exudate within, and only an occasional leukocyte about the bile channels. The Kupffer cells are not prominent.

Best's carmin stain shows fine red-staining droplets within the liver cells. The larger, and more vacuolated cells contain fewer of these. The cells of some of the bile channels, especially those of smaller order, show similar changes. Red-staining droplets are also found within the lumen of the larger biliary ducts. Glycogen is not present in any of the nuclei, and only a very occasional Kupffer cell contains this substance.

In portions of the section in which the fixation is not quite satisfactory, intercellular spaces, as well as intracellular bile canaliculi are seen outlined against the clear background. These portions resemble a preparation stained for bile capillaries.

The cells within the capsule of the liver contain glycogen.

The Sudan stain on frozen sections reveals neutral fat, chiefly in the cells of the periportal areas.

Kidney. Only portions of the kidney were obtained, and the weight could not be determined. The yellowish-gray cortex and the darker gray medulla are well delimited.

Microscopic Examination. Hematoxylin-eosin stain: Many of the glomeruli retain their fetal form. Some of the cells of the proximal convoluted tubules have a granular, others a clear cytoplasm. The lining

FIG. 1.—Anterior view. Both ventricles form the anterior surface of the heart. Lungs are left attached for comparison with the size of the heart.

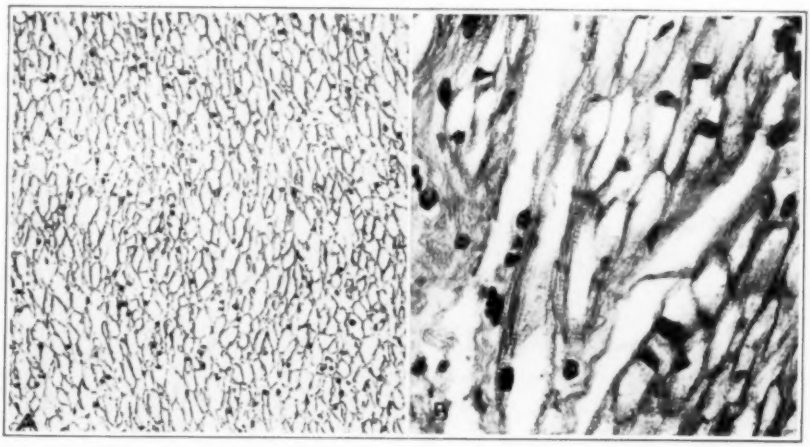

FIG. 2*A*.—Myocardium. Low-power view, showing the cytoplasmic network (hematoxylin-eosin stain).

FIG. 2*B*.—Myocardium. High-power view of an area in which the fibers are cut tangentially, showing hollow cylinders with striations in the muscular wall (iron-hematoxylin stain).

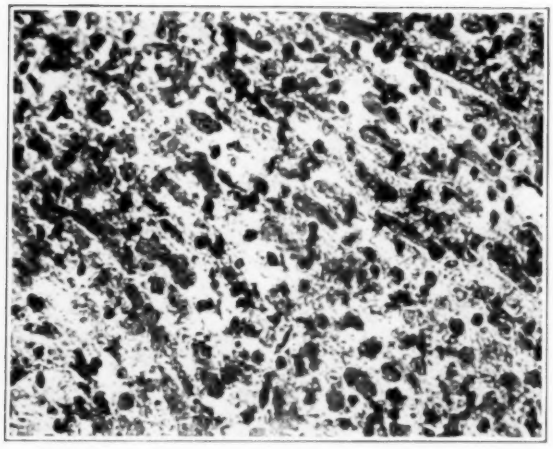

FIG. 3.—Myocardium. High-power stained with Best's carmin method. The gray rods and droplets correspond to the red staining glycogen.

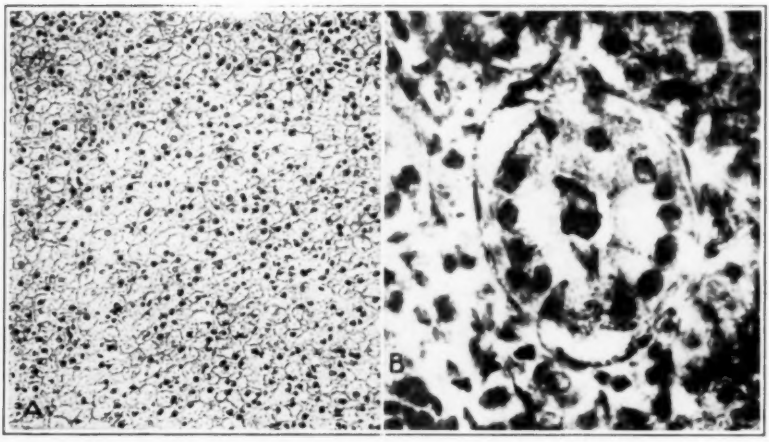

FIG. 4*A*.—Liver. Low-power view.

FIG. 4*B*.—Kidney. Best's carmin stain, showing droplets of glycogen within the cells and a mass of glycogen in the lumen of a collecting tubule.

cells are swollen, bulge into the lumen, and in many places completely occlude it. The cytoplasm of the cells of the proximal portion of the descending loop of Henle is similar in appearance, but not quite as abundant. The ascending loops are diffusely pink-staining. The cytoplasm of the distal convoluted tubules, the collecting and the uriniferous tubules is similar to that of the proximal convoluted tubules. The bloodvessels are thickened. Best's carmin stain reveals glycogen in many of the glomeruli, in Bowman's space, and also within the cells lining the capsule, also within the cells of the proximal convoluted tubules, the distal convoluted tubules, the collecting tubules, and the uriniferous tubules. Very little glycogen is present within the lumen of these structures until the collecting tubules are reached, where an appreciable amount is seen (Fig. 4-*B*).

Lungs. There is an area of bronchopneumonia in the right upper lobe.

Thymus. There is necrosis in the center of many of Hassall's corpuscles. Glycogen is present within many of the cells, especially the peripheral layers of the corpuscles.

Chemical Analysis of Organs. The formalin fixed material was placed in absolute alcohol 4 weeks after the autopsy. Analyses of the heart, liver, kidney and lungs were done by Pflüger's method. In spite of the fact that the specimens had been in 10% formalin for so long a period, the following amounts of glycogen were found: Heart, 3.57%; liver, 3.25%; kidney, 4.34%; lung, 0.32%.

Of these organs the only one which normally contains glycogen in substantial amounts is the liver. The chemical findings corroborate the histologic demonstration of glycogen, so that we are undoubtedly dealing with a case of abnormal glycogen storage in the von Gierke's sense. The formalin fixation precluded investigation of the glycogen ferments.

Discussion. Von Gierke's disease, or glycogenosis, is a metabolic perversion characterized by abnormal deposition (or storage) of glycogen, analogous to the abnormal storage of kerasin and other lipoids in those well-studied errors of fat metabolism, Gaucher's disease and Niemann-Pick's disease. Yet, the analogy must not be pressed too far, as the latter represent definite storage preponderantly in the reticuloendothelial system. In the present disease the reticuloendothelial system is singularly free, the parenchymatous elements being the ones chiefly involved. The mechanism responsible still remains to be elucidated.

A persistence of the fetal type of glycogen metabolism into postnatal life is probable. It is known that fetal glycogen does not disappear so rapidly by spontaneous glycogenolysis, and cannot be mobilized readily by cold or adrenalin.[6, 8] In the fetus, glycogen deposits in the kidneys, bloodvessels, and organs of internal secretion are present, but in extrauterine life the occurrence of glycogen in these sites is strictly pathologic.

The biochemical etiology of this disease is still obscure. Against the assumption that the glycogen itself is chemically different or biologically inert, evidence is presented by Schoenheimer that glycogen isolated from a case of this disease had the usual physical

and chemical properties, and could be hydrolyzed by normal liver tissue. The complete absence of glycogenolytic enzyme in the diseased liver seems unlikely. On the other hand, increased amounts of amylase were observed in the urine of some of these cases. The amylase titer of the serum in this condition deserves further study; the glycogen content of the serum is occasionally reported as increased. Thus it seems that the glycogen storage is neither due to a qualitative variation of the glycogen, nor to a lack of glycogenase, but to an unexplained inability of the enzyme to act on its substrate. This may be due either to the presence of inhibitory substances, or to the absence of activators, or to the fact that the enzyme has no access of the substrate.

Deposits of glycogen may occur in the liver, kidneys, brain, heart, bloodvessels, muscles, and organs of internal secretion. The clinical picture depends upon the sites of deposition and upon the extent to which the vital processes of the affected tissues are interfered with. So far three main symptom groups are known, due to preponderance in liver and kidneys, in heart and bloodvessels, or in the brain. The first is the best known and possibly the largest group—the hepatonephromegalia glycogenica of von Gierke. The second group—that with cardiac hypertrophy—gives a clinical picture which, in the absence of proper chemical and histologic studies, may be confounded with the so-called idiopathic hypertrophy of the heart, as pointed out by Pompe.[4]

It is possible that many of the cases formerly classified as idiopathic hypertrophy belong to the von Gierke type of disease with enlarged heart, and that rhabdomyomata are localized collections of glycogen-rich fibers, possibly due to focal disturbance in glycogen metabolism. Virchow first recognized the relationship between so-called idiopathic hypertrophy and rhabdomyoma of the heart. As far back as 1900, Marchand[10] and Askanazy[11] pointed out that rhabdomyomata of the heart were rich in glycogen. Schmincke[12] described the transition between isolated and diffuse rhabdomyoma of the heart and considered this a persistent embryonal state giving rise to hypertrophy. In many cases of the so-called idiopathic hypertrophy vacuoles have been noted in the heart muscle but were not explained and their association with large livers and enlarged kidneys is frequent. Sprague, Bland and White[13] report enormous enlargement of the heart with vacuolization of the muscle fibers, as well as vacuolization of the hepatic cells. They do not explain these changes, typically those of glycogenosis, which apparently was not suspected.

The third group, *i. e.*, with cerebral symptoms due to glycogen deposits in the brain and spinal cord (Kimmelstiel[14]) makes necessary a review of all poorly understood cerebral conditions in children in order to determine whether some of them are not related to the effect of abnormal glycogen storage.

Summary. A case of von Gierke's disease with a markedly enlarged heart is presented. The possible relationship of this malady to idiopathic hypertrophy of the heart and diffuse rhabdomyoma of the heart is discussed.

After the presentation of this paper we were informed by Dr. K. Kato that he had observed 2 similar cases in Chicago.

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THE EFFECT OF ELEVATED METABOLISM ON THE HEART OF FRIZZLE FOWL. II. INCREASED RATIO OF HEART TO BODY WEIGHT.

By Ernst P. Boas, M.D.,
NEW YORK CITY,
AND
Walter Landauer, Ph.D.,
STORRS, CONN.

(From the Medical Service (Dr. George Baehr) Mt. Sinai Hospital, and the Storrs Agricultural Experiment Station.)

In a previous communication[1] it was pointed out that Frizzle fowl, a variety of chicken with scanty plumage, offer an opportunity of studying the effect on the heart of the increased basal metabolism, resulting from the profound disturbance in the conservation of body heat. It was shown that the heart rate of Frizzle hens is on the average 72 beats (27%), and of Frizzle roosters 117 beats (68%) above that of normal chickens. The conclusion was reached that the rapid heart rate of Frizzle fowl is conditioned by their elevated metabolism.

One of us (Landauer) had noted that the hearts of Frizzle fowl appear hypertrophied, elongated and relatively narrow. The following observations comprise a verification of this impression.

Method.—The study of heart weights is a difficult and painstaking procedure, and the results depend a good deal on the technique employed. In

our study an additional handicap lay in the fact that the birds were killed in Storrs, and their hearts weighed in New York City.

The determination of accurate heart weights involves the careful freeing of the heart of epicardial fat, bloodvessels and pericardium, and the establishment of a ratio between heart weight and body weight. This was first stressed by Müller.[2]

We followed the following procedure: The birds were weighed and immediately thereafter killed at Storrs. Then the heart was removed, and the gross weight of the undissected heart was recorded. The heart was then placed in 10% formaldehyde solution and was shipped to New York. Hermann[3] has shown that a heart in 10% formaldehyde gains in weight during the first 2 to 4 days, and then gradually returns to the original autopsy weight in 6 to 10 days. For several days following there is very little change in weight. Thus, if a heart that has been placed in formalin is weighed between the 10th and 15th day after immersion into the solution, its weight will closely approximate the weight in the fresh state. Kirch[4] made similar observations and demonstrated that the weights of the different chambers as well as their linear measurements change proportionately when the heart is fixed in formalin solution. As is shown in the tables, our chicken hearts were weighed and dissected at a time when their weights closely approximated their original fresh weights.

The actual procedure and dissection was carried out in the following manner. The heart was removed from the formalin solution and gently dried with a cloth. Any excess solution was gently expressed from the auricles. The whole heart was then weighed. A balance which was accurate to 0.1 gm. was employed for all of the weighing. In the chicken heart the fat is collected particularly in the auricoloventricular groove and at the roots of the aorta and pulmonary artery. This was carefully dissected away. The large vessels were left in place. Any excess fat in the epicardium was removed. The auricles were then separated from the ventricles by blunt dissection, leaving the upper surfaces of the ventricles perfectly smooth with intact musculature. An incision was then made down the posterior wall of the right ventricle along the septum. This incision is marked by a posterior descending branch of a coronary artery. Both the artery and the incision curve downward and reach the lower border of the right ventricle at a point about $\frac{3}{5}$ of the distance from the root of the aorta to the apex of the heart. The incision was then continued to the left and then upward along a line formed by the extreme limit of the cavity of the right ventricle and along the anterior border of the interventricular septum to and through the auriculoventricular ring. The root of the pulmonary artery and the aorta were then separated by blunt dissection along a line of natural cleavage. This cleavage was continued on the right ventricular aspect of the interventricular septum, and was marked by small deep septal branches of the coronary arteries,[5] so that the musculature of the conus arteriosus was dissected free as part of the right ventricle. The pulmonary artery was then cut off just above the semilunar valves. The left ventricle was then opened by a cut along the posterior border of the septum paralleling the first cut of the right ventricle. The septum was then cut away along the line of attachment of the right ventricle. The aorta was cut off just above the semilunar valves.

The following weights were recorded: the undissected uncleaned heart, the cleaned heart, the auricles together, the right ventricle, the left ventricle, the interventricular septum.

Even in the hearts of humans and of large animals there has been great difficulty in establishing proper incisions that would lead to accurate separation of the cardiac chambers. The chief stumbling

block has been to determine how much of the interventricular septum belongs to the right, and how much to the left ventricle. Müller calculated that about 30% of the septum belongs to the right, and 70% to the left ventricle. Subsequent workers have criticized his technique and his calculations. Wideroe[6] avoided the dilemma by ignoring the septum and using only those portions which were free of the septum. He thus established his ratio of right ventricle to left ventricle. Both Lewis[7] and Hermann[3] attempted to improve on these methods by carefully worked-out dissections. Such painstaking dissection, difficult enough in a large heart, is impossible to carry out with accuracy in the small hearts of chickens: so we adopted a rougher method, which more closely approximates the original one of Müller. We do not lay undue weight on our findings, therefore, insofar as the relative weights of the individual chambers are concerned, although results are sufficiently uniform to appear significant. The auricular weights are not always accurate, for not infrequently in removing the heart, part of the right auricle was cut off. We would lay particular emphasis on the combined weight of the two ventricles including the septum, for these are absolutely accurate.

It is well recognized that absolute heart weights have little significance, and that it is necessary for purposes of comparison to establish the ratio between heart weight and body weight. In the case of birds, it is advisable to deduct from the body weight the weight of the feathers, for the heart weight is proportional primarily to the weight of the skeletal musculature (Wideroe). Relying on the studies of Mitchell, Card, and Hamilton,[8] we have arbitrarily estimated that in fully grown normal birds the plumage constitutes 8% of body weight in males, and 7% in females. For the Frizzle fowl we estimate the plumage as 5 grams, except for the lot of birds killed on October 16, 1933. For some reason these birds had a better developed plumage. For them we assumed a plumage weight of ½ of that of normal chickens.

The hearts of 110 chickens were weighed. Of these 37 were normal females, 33 Frizzle females, 20 normal males, and 20 Frizzle males. The normal chickens were mostly Leghorns, with a few creepers and rumpless forms. The data, arranged according to body weight, appear in Table 1.* Table 2 presents the averages of the ratios: total cleaned heart weight times 1000, divided by body weight without feathers; total ventricular weight times 1000 divided by body weight without feathers; right ventricle divided by left ventricle including the septum; and right ventricle divided by the left ventricle, with the septum excluded. To the averages are appended the standard deviations from which the errors of the differences can be readily calculated.

* Because of lack of space the detailed protocols cannot be printed. The individual figures will be supplied by the authors on demand.

TABLE 1.—HEART WEIGHTS AND RATIOS.

Breed and sex.	Number of chickens.	Average body weight, grams.	Average body weight without feathers, grams.	Average heart weights.							Average ratios.			
				Uncleaned.										
				Fresh, grams.	Fixed, grams.	Cleaned, grams.	R V, grams.	L V, grams.	S, grams.	As, grams.	$\frac{H \times 1000}{B}$	$\frac{V \times 1000}{B}$	$\frac{LV + S}{RV}$	$\frac{RV}{LV + S}$
Normal females	8	1000	931	5.4	5.3	3.6	0.5	1.8	0.7	0.6	3.9	3.2	0.21	0.30
Normal females	9	1214	1127	6.1	6.0	3.9	0.6	2.0	0.7	0.7	3.4	2.9	0.22	0.30
Normal females	10	1400	1302	6.2	6.1	3.9	0.6	2.0	0.7	0.6	3.0	2.6	0.23	0.31
Normal females	10	1720	1600	8.0	7.8	4.8	0.7	2.4	0.8	0.8	2.9	2.5	0.22	0.30
Frizzle females	13	1239	1211	7.0	6.8	4.9	0.8	2.5	1.0	0.7	4.2	3.5	0.22	0.31
Frizzle females	10	1650	1603	8.3	8.2	5.8	0.9	2.8	1.2	0.9	3.6	3.1	0.24	0.34
Frizzle females	10	2036	2006	11.3	10.8	8.2	1.3	4.0	1.8	1.1	4.4	3.6	0.23	0.33
Normal males	10	1653	1521	8.2	8.2	6.6	1.0	3.6	1.0	0.9	4.3	3.7	0.23	0.30
Normal males	10	1924	1771	9.9	9.8	7.8	1.3	4.1	1.1	1.2	4.4	3.6	0.25	0.31
Frizzle males	10	2036	1963	13.5	13.3	10.5	1.4	5.6	1.8	1.6	5.3	4.5	0.20	0.27
Frizzle males	10	2562	2469	14.4	14.2	10.6	1.7	5.0	2.1	1.8	4.3	3.6	0.24	0.35

R V = right ventricle; L V = left ventricle; S = Septum; As = auricles; H = total cleaned heart weight; V = ventricular weight; B = body weight without feathers.

TABLE 2.—HEART RATIOS OF NORMAL AND FRIZZLE FOWL.

	No. of chickens.	$\frac{H \times 1000}{B}$ Aver.	σ	$\frac{V \times 1000}{B}$ Aver.	σ	$\frac{RV}{LV + S}$ Aver.	σ	$\frac{RV}{LV}$ Aver.	σ
Females: Normal	37	3.3	± 0.50	2.7	± 0.4	0.22	± 0.03	0.30	± 0.05
Frizzle	33	4.0	± 0.88	3.4	± 0.68	0.23	± 0.05	0.33	± 0.07
Males: Normal	20	4.2	± 0.36	3.6	± 0.28	0.24	± 0.03	0.31	± 0.05
Frizzle	20	4.8	± 1.3	4.0	± 1.1	0.22	± 0.06	0.31	± 0.13

H = heart weight; V = ventricular weight including septum; R V = right ventricle; L V = left ventricle; S = Septum; B = body weight minus feathers.

There are few available studies of the heart weights of chickens. Loer,[9] employing Müller's method, weighed the hearts of 9 male and 13 female chickens aged 4 to 5 months. The ratio heart weight times 1000 to body weight was 4.1 for males and 3.8 for females. Wagner[10] found that this ratio varied from 3.8 to 7.7. Ehrich and Cohn[11] report relative heart weights of 12 female Rhode Island Reds ranging in age from 1 to 8 years and find the heart-weight-body-weight ratio to be on the average 3. All of these figures correspond rather well to our total heart-weight ratios.

We wish to call attention particularly to the ratio of the total ventricular weight to the body weight, for this is the most accurate of our determinations. The difference between the averages of $\frac{V \times 1000}{B}$ of normal and Frizzle females is 0.7 with an error of ±0.14. This difference is significant, so one may conclude that in proportion to body weight, the ventricles of Frizzle pullets are heavier

than those of normal pullets. The error of the difference of the male series is greater, so that taken alone, the figures would have no significance; but in view of the fact that they differ in the same direction as do the females, it seems safe to infer that the ventricles of Frizzle cockerels are heavier than those of normal cockerels. The variability of the whole heart ratios is greater, but they too behave in the same manner. The conclusion is justified that the hearts of Frizzle fowl, in relation to their body weights are heavier than those of normal fowl. The ratios between right and left ventricles, whether or not the septum be included, are practically the same for Frizzle and normal fowl. It seems, therefore, that both ventricles share equally in the hypertrophy that takes place.

A study of Table 1 reveals no significant difference between chickens under 1, and over 1 year of age in the ratio of ventricular weight to body weight. Nor is there a constant difference in this ratio if one compares smaller with larger chickens of the same sex and breed. It is strikingly evident that the heart-weight-body-weight ratio of Frizzles is much more variable than that of normal fowl. This is due undoubtedly, to variation in the amount of plumage, and in the reaction of the bird thereto.

The relative heart weights, whole heart to body weight as well as ventricular weight to body weight of males, both normal and Frizzle, are greater than those of females.

Our findings of cardiac hypertrophy in Frizzle fowl are consistent with those reported in our previous paper[1] that the heart rates of Frizzle fowl are more rapid than those of normal fowl. It would appear that this cardiac hypertrophy, as well as the tachycardia are conditioned only by the high metabolism of the Frizzle fowl.*

The fact that an increased metabolism alone may cause functional and organic changes in the heart (tachycardia and ventricular hypertrophy) is of theoretical interest, as well as of practical importance, particularly in respect to the cardiac disorders of hyperthyroidism. Other evidence is available that an increased metabolism may add to the work of the heart. Hall and Tainter[12] have shown that the administration of dinitrophenol, a drug that increases the metabolism without the intermediation of the thyroid gland, may cause a considerable increase in the volume output of blood per minute. Smith and MacKay[13] fed albino rats active thyroid material, and found that when the basal metabolic rate is so varied, a linear relationship exists between the heart rate and the basal metabolic rate. They further found a direct relationship between food intake and heart weight and pointed out that "this strengthens the view that heart weight is directly related to total metabolism and hence to volume flow of blood." These observations suggest a close

* Experimental work now in progress confirms this conclusion.

analogy to our findings in Frizzle fowl in whom both food consumption and metabolism is greater than in normal chickens.[1] Simonds and Brandes[14] noted cardiac hypertrophy involving all of the chambers in dogs that were fed large amounts of thyroid extract. Minot and Means[15] showed that in chronic lymphatic leukemia, in which there is an increased metabolic rate unassociated with hyperthyroidism, the pulse rate is elevated, and that the hearts examined postmortem were on the average 75 grams overweight.

Summary. Frizzle fowl, a variety of chicken with scanty plumage and resultant high basal metabolism, permit the study of the effect of increased basal metabolism, as such, on the heart. The heart weights of 57 normal and 53 Frizzle fowl were determined by a modification of Müller's method. The ventricular weight relative to body weight of Frizzle fowl is significantly greater than that of normal fowl. Both ventricles share equally in this hypertrophy. These observations, together with our previous demonstration of the existence of more rapid heart rates in Frizzle fowl, indicate that an increased metabolism alone may cause functional and organic changes in the heart (tachycardia and ventricular hypertrophy). They suggest that in Graves' disease, the elevated metabolism, by increasing the work of the heart, directly contributes to the cardiac disturbances that are so commonly observed.

We wish to acknowledge the technical assistance of Mrs. Helen S. Boas.

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FAMILIAL CLEIDO-CRANIO DYSOSTOSIS.*

JULIANNA R. TATUM, M.D.,
PHYSICIAN-IN-CHIEF, PEDIATRIC OUT-PATIENT DEPARTMENT, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

(From the Pediatric Out-patient Department.)

ALTHOUGH defective clavicles were described by Martin as early as 1765, it was not until 1897 that Marie and Sainton further described and named the defect Cleido-cranio Dysostosis.

In 1902 Paterson published observations to show that the clavicle is developed in two portions: the outer part ossifies in membrane before cartilage formation takes place, the inner ossifies in cartilage. The clavicle is the first bone to ossify in man. A center appears in the 5th week or earlier—before a cartilaginous basis has begun to form; Fawcett demonstrated an embryonic clavicle in a 17-cm. fetus. The pathogenesis of this condition is obscure. Jansen of Leyden in 1921 suggested that a small amniotic sac exerted pressure on the growing cells, and caused congenital defects according to the time this occurred, but of course the hereditary factor must be borne in mind. The defect in the clavicles may range from a break in continuity simulating an ununited fracture to complete absence of both bones.

The cranial vault and facial bones also often present abnormalities. There is an increase in girth and breadth of the skull giving a cephalic index greater than normal, while the facial measurements are below the average. The frontal and parietal eminences are unduly large, the sutures and anterior fontanelle remain open. The palate is highly arched, with a median furrow; the inferior maxilla is prognathous; the teeth are late in erupting and are incomplete and irregular in development and setting.

The phalanges are shorter than normal. There is frequently a spina bifida, and occasionally defects in the ribs and coccyx.

The height is below normal average giving the appearance of mild dwarfism. There is generally no disability from the defective clavicles, and rarely is pain caused by pressure of the clavicular stumps upon bloodvessels or nerves beneath.

The sex frequency is apparently equal. Fathers or mothers may transmit the condition to sons or daughters, and it may involve three or four generations. However, isolated cases are not rare.

Lues is not a causative factor, and associated diseases, such as tuberculosis, are negligible. Early rickets is found in some cases, although many are diagnosed as such before the true state is discovered.

* Read before The Philadelphia Pediatric Society, January, 1934.

Case Abstracts. CASE 1.—On February 6, 1933, Harry E. was brought to our clinic because he was thin and small for his age. He was a white boy, aged 7, height 41½ inches, weight 38½ pounds. He was pale but not acutely ill. Temperature 99 axilla, pulse 96, respirations 26. His head was large with prominent frontal and parietal eminences, and obvious grooves between these bones. The anterior fontanelle was open, and the vertex distinctly flattened. His face was small and receding in comparison with the cranium. The root of the nose was depressed and broad, the eyes set far apart, the lower jaw small and chin pointed.

The eyes, nose and ears were grossly negative. The palate was highly arched with a deep median furrow from the dental arch to the soft palate. The teeth were irregular and crowded; only 3 upper and 3 lower incisors were present and no permanent teeth had erupted. The tonsils were small and cryptic.

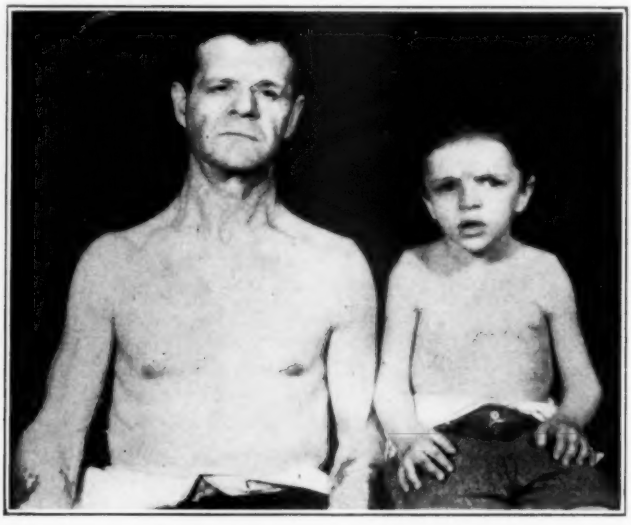


FIG. 1.—Two cases of cleido-cranio dyostosis. Harry, age 7 years, and his father, showing conformation of head and chest.

His chest was thin, with sloping shoulders and depressed sternum, especially at the xyphoid. No clavicles were palpable. The lower ribs were flared but there was no Harrison's groove or rachitic rosary. The scapulæ were small but prominent. The lungs were resonant and breath sounds physiological. The heart was not enlarged; no murmurs elicited.

The abdomen was somewhat distended but soft. The liver was palpated 1 inch below the costal margin; no other organs or masses felt; no tenderness elicited.

His extremities were thin, no apparent disability or weakness, in fact, he was delighted to perform several contortionist stunts. His hands and feet stubby with short thumbs. No epiphyseal enlargement noted.

The Roentgen ray reports are as follows: "The right clavicle is entirely absent and only a small, rudimentary inner portion of left clavicle is visualized. Lung fields appear normal. Diaphragms are clearly visualized. The heart is not enlarged. The head is square-shaped. The anterior fontanelle is very wide and open. There is considerable thinning of the plate of the

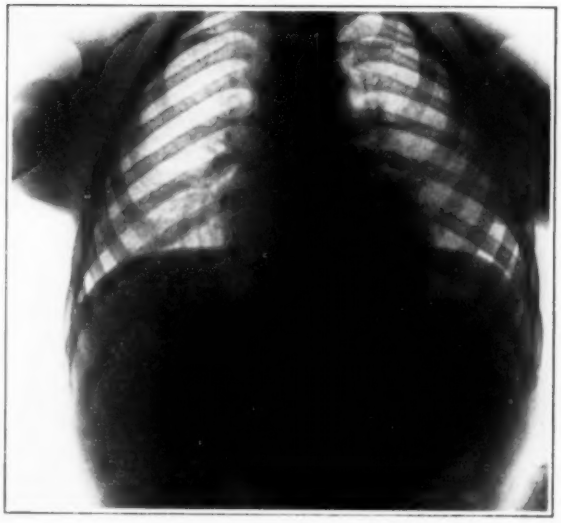


FIG. 2.—Roentgen ray of chest showing absence of right clavicle and rudimentary inner portion of left clavicle.

FIG. 3.—Roentgen ray of skull showing the open fontanelle, and non-union of the lower jaws at the symphysis.

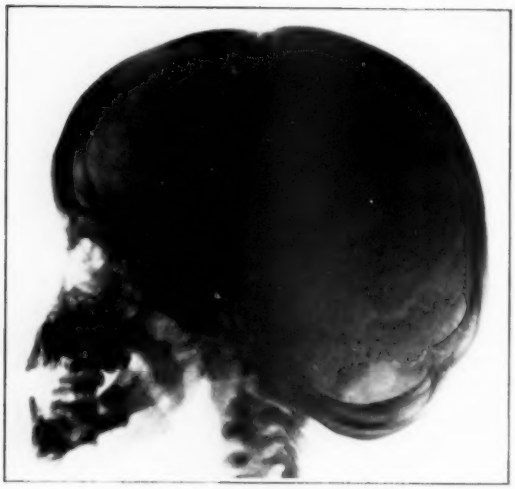


FIG. 4.—Lateral view of skull. This shows thinning of the plate of the frontal bone and widening of the sutures. The posterior portion of the skull drops below the usual level at the foramen magnum.

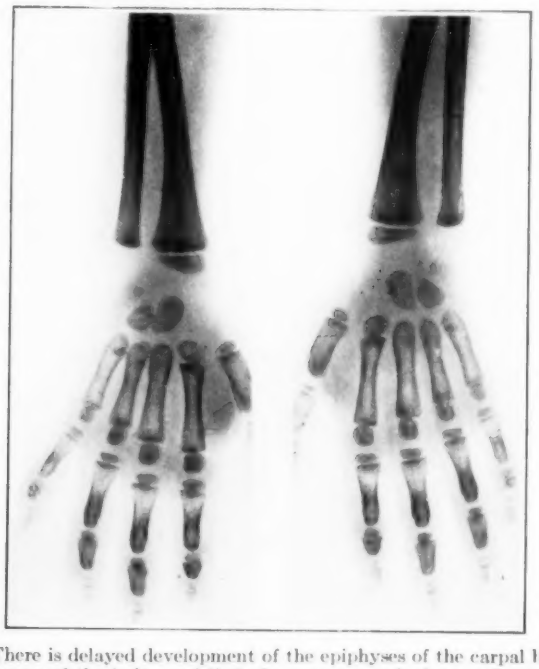


FIG. 5.—There is delayed development of the epiphyses of the carpal bones. The second phalanges of the index and little fingers are much shorter than normal and somewhat irregular in outline.

frontal bone. There is some widening of the sutures. The sella turcica appears normal. There is non-union of the lower jaws at the symphysis. The septum is considerably deflected to the right. There is delayed development of the epiphyses of the carpal bones. The second phalanges of the index and little fingers are much shorter than normal and somewhat irregular in outline." Diagnosis: Cleido-cranio dysostosis.

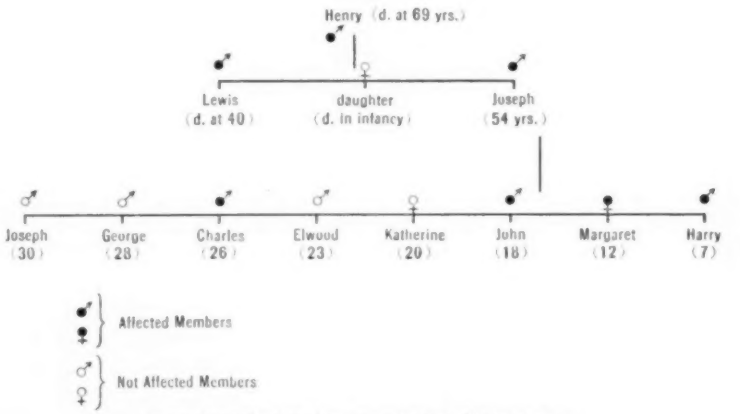
The blood calcium was 10.4 mg. per 100 cc.; phosphorus was 3.9 mg.

Past History. The patient was born in Philadelphia, full term, breech delivery. It is noted that he "was unable to move arms at all for 3 weeks. At 3 months he was admitted to the Babies' Ward of this hospital, because of failure to gain weight. His condition was immediately recognized and confirmed by Roentgen ray.

Much of the next 9 months was spent in the hospital. He gained weight slowly, reaching 14 pounds 12 ounces at 11 months. His skull increased to a circumference of 17 inches, with the anterior fontanelle large and tense, 3 by 4½ inches. Both the blood and spinal fluid Wassermann tests were negative, but he was given mercurial inunctions for 3 weeks. No other blood studies were made.

During 1927, 1928, and 1929, he was in fairly close touch with the clinic. In 1928 he had measles, pneumonia and pleurisy. His blood Wassermann test was again negative.

Chart 1.



The numbers in brackets show the present ages of living members.

At 2 years he weighed 22½ pounds; at 3, 25½ pounds; height 32 inches; at 4, 27 pounds, height not recorded; at 4¾, 29½ pounds, height 36 inches; at 6, 33 pounds, height 38 inches; at 7, 38½ pounds, height 41½ inches.

His present measurements are normal for 5 years.

This yearly increase in weight and height compares favorably with the normal average for ages 5 to 7 inclusive. Although he has always been short for his age, his weight has corresponded with his height according to Woodbury's tables (U. S. Dept. Labor).

Family History. Harry is the youngest of 8 siblings, all living. There have been no miscarriages nor stillbirths. Of the 8 children, 3 boys and 1 girl have defective clavicles, abnormal skulls, and malformed teeth. The father, Joseph, has rudimentary clavicles, and his brother, who died unmarried at 40, resembled him. The only other member of that generation

was a sister who died in infancy, condition unknown. Joseph's father had no clavicles, but nothing is known of his grandfather or of collateral branches of the family. Thus we have a history of 3 generations including 7 affected members. The family tree given below starts with the patient's grandfather and represents all of his descendants.

This family is of Pennsylvania stock, English descent, sturdy and able to do vigorous work. Joseph is a pipe fitter employed by the Westinghouse Company, his brother Lewis was a sailor and died by drowning. The father, 6 sons, and 1 of the 2 daughters, have been studied and the following data collected.

CASE 2.—Joseph, Sr., aged 54, shows that "both clavicles are rudimentary. The scapulæ are much smaller than normal, elevated; the chest is sort of barrel-shaped. The heart is not enlarged. Arch of aorta shows some evidence of arteriosclerosis, and the diaphragms are clearly visualized. The terminal phalanges are much smaller than normal. The epiphyseal line of the lower radius is still demonstrable but is united. All the carpal bones are present. The right frontal sinus is absent. The left one is somewhat smaller than normal. The septum is deflected to the left. There is no evidence of any unerupted teeth. The sella turcica is normal in shape and outline; not enlarged; no evidence of intracranial pressure. Suture lines are well outlined showing evidence of calcification." Roentgen-ray report March 13, 1933.

The blood Kahn test was negative; blood calcium, 10.2 mg. per 100 cc.; blood phosphorus, 3.3.

CASE 3.—Joseph, Jr., aged 30, known to medical clinic. "Typical neurasthenic." "The clavicles appear normal. The scapulæ are normally outlined; lung fields and cardiac silhouette are normal. The sella turcica is normal in size and outline. The suture lines are normal. There are several unerupted teeth in upper jaw; otherwise the maxillæ and mandible appear normal." (Roentgen ray report March 10, 1933.)

CASE 4.—George, aged 28, apparently normal white male. "The clavicles appear normal. Scapulæ are well-formed. The ribs and lung fields are normal. The heart is not enlarged. Sella turcica is normal in outline. There is no evidence of intracranial pressure. Suture lines appear normal. There are several unerupted teeth in the upper and lower jaws." (Roentgen ray report March 6, 1933.)

Blood calcium 13.8 mg. per 100 cc.; phosphorus, 2.5.

CASE 5.—Charles, aged 26, distinct type of cleido-cranio dysostosis. "This is another case of cleido-cranio dysostosis, described previously in other members of the family, showing abnormal development of the clavicles and under development of the scapulæ. Numerous unerupted teeth and non-union of the superior maxilla with an ectopic frontal suture, widening and squaring of the head and non-union of the suture lines. Sella is normal in size." (Roentgen ray report March 13, 1933.)

Blood calcium 10.7 mg. per 100 cc.; phosphorus 2.2.

CASE 6.—Elwood, aged 23, pipe fitter, apparently normal male. "The clavicles and bones of the skull do not show the typical findings we have noted in the other members of the family. Both clavicles are normally formed. There is no evidence of undescended teeth and the bones of skull appear normal." (Roentgen ray report March 13, 1933.)

Blood calcium 10.7 mg. per 100 cc.; phosphorus 2.5.

CASE 7.—John, aged 18, full term, normal delivery, birth weight 9 pounds. He had the usual childhood diseases. He first came to the clinic June 20, 1927, aged 12½ years.

The *physical examination* at that time is as follows: "Bosses enlarged. Nose stubby and bridge typically that of adenoids. Tonsils cryptic; not overly enlarged. Shoulders sloping. Funnel-chested. Slight marks of

rachitic rosary. Heart slight heave. No thrill. Marked impulse 5th and 6th interspace below nipple, size of a quarter. Soft blowing quality 1st sound. P2 > A2. Sinus arrhythmia. No murmurs. Chest and abdomen otherwise negative. Nails are some of them curved."

On September 26, 1927, there is a note "No complaints. . . . Edentulous and lacking outer half of clavicles."

June, 1927, weight 67 pounds; September, 1927, 70½ pounds; April, 1928, 73¼ pounds; height 51 inches (normal height for 9 years).

Roentgen ray taken March 13, 1933: "This is another case of cleido-cranio dysostosis, described previously in the other members of the family, showing the abnormal development of the clavicles and underdevelopment of scapulæ. Numerous unerupted teeth and non-union of the superior maxilla with an ectopic frontal suture, widening and squaring of the head and non-union of the suture lines. Sella is normal in size."

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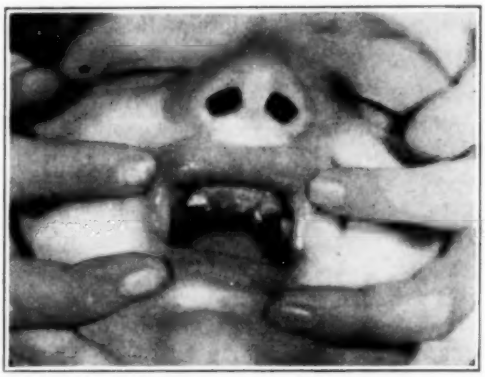

FIG. 6.—Margaret, age 12 years, showing eruption of permanent incisors behind deciduous teeth.

CASE 8.—Margaret, aged 12, height 55¼ inches, weight 102 pounds, short, obese, white girl not yet adolescent. Her head is large, with prominent frontal bosses and a broad low forehead. The anterior fontanelle is apparently closed. The eyes are set far apart, but otherwise grossly negative. The nose and ears are normal. The chin is small and pointed, the palate highly arched, with a deep groove from the incisors to the soft palate. The tonsils are small. The teeth are irregular, poorly formed and carious. The second set of incisors are erupting behind the deciduous teeth which are still present.

There is no cervical adenopathy, but the thyroid is palpable. Her chest is round and obese. There is a partial clavicle palpable on the left and a stub attached to the sternum on the right. The lungs are clear and the heart apparently normal. The abdomen is obese, no tenderness nor rigidity, no masses nor organs palpable. Her hands and feet are stubby, with short thumbs. There is no evidence of old rickets.

"There is only a small rudimentary portion of the right clavicle present, and a somewhat larger rudimentary clavicle on the left side. On the right side just the inner third is demonstrable and on the left side the inner two-thirds is visualized. The lung fields appear normal. Diaphragms are clearly visualized. The heart is not enlarged. The head is square-shaped. There is some widening of the sutures. The anterior fontanelle is still open.

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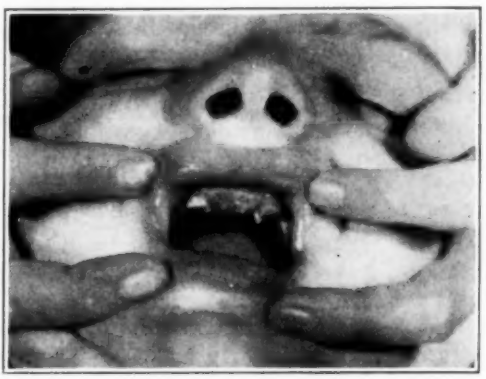

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There is considerable thinning of the vault in this area. There is non-ossification of the lower jaws at the symphysis. There is delayed dentition, and the terminal phalanges have a peculiar rounded effect. There is an ectopic suture in the frontal lobe." (Roentgen ray reports.)

Blood calcium 10.8 mg. per 100 cc.; phosphorus 4.5.

Margaret had a normal delivery at full term. Birth weight 8½ pounds. She had the usual childhood diseases before she was 6, as well as diphtheria and pneumonia. She first came to the clinic in 1927 and was a fairly regular visitor for 3 years. Her most common complaint was nausea and vomiting with abdominal pain, and several times appendicitis was considered. Her Wassermann test was reported negative in both antigens. It is interesting that there is no mention of any bony abnormality during this period, although with 2 brothers both known to be without clavicles, attending clinic at the same time, it seems strange that it was unnoted. No Roentgen ray was taken at that time.

March 14, 1933, B. M. R., +18.

1927, weight 44 pounds, height not recorded; 1929, 52 pounds, height not recorded; 1930, 64 pounds, height 50 inches; 1933, 102 pounds, height 55¼ inches.

Discussion. Of the 144 cases reviewed by Stocks in 1925, not one mentions blood studies other than Wassermann tests. Fitchet, in 1929, gives the figures of blood calcium and blood phosphorus on 1 case and reports 2 other cases as being "within normal limits." Malmberg, in 1932, reports a sporadic case, with a blood calcium of 10.8 and blood phosphorus of 3.8, and quotes Klinke and Pahlke, who, in 1930, studied 2 cases with similar results.

These 4 cases are all that I can find in the literature on which blood studies have been reported. To these I have added the figures on our patients, which tally closely and I believe are significant. In children the normal blood calcium, according to Levinson, ranges from 10 to 11.5 mg. %, and the phosphorus from 4.8 to 6.8 mg. %. In these patients there is a decided lowering of the latter, while the calcium maintains a normal level.

TABLE 1.—BLOOD CALCIUM AND PHOSPHORUS FINDINGS IN 11 SUBJECTS.

Patient.	Age, years.	Blood calcium.	Blood phosphorus. (Normal 5 mg.)
Children.			
1. Malmberg's case	3	10.8	3.8
2. Klinke and Pahlke's Case 1	3¾	12.1	3.8
3. Case 2	4¾	11.8	2.9
4. Fitchet's case	10	10.1	4.4
5. Harry	7	10.4	3.9
6. Margaret	12	10.8	4.5
Adults.			(Normal 3 mg.)
7. John	18	11.6	2.8
8. (Elwood)	23	10.7	2.5
9. Charles	26	10.7	2.2
10. (George)	28	13.8	2.5
11. Joseph, Sr.	54	10.2	3.3

The two patients in parentheses did not have the dysostosis.

Most of the children suffering with this condition are diagnosed as cases of rickets, for the clavicular defect is not apparent and the square head with prominent bosses is noticed at a glance.

Like many other defective conditions supposed to be rare until we look for them, cleido-cranio dysostosis probably is more common than we suspect. Much more study must be done before we can draw definite conclusions from this family, but I believe it significant that Harry's retardation of growth occurred within the first 2 years of life, and that there is a definitely low blood phosphorus.

If sporadic cases could be recognized early, and if affected families could be watched and possibly prenatal treatment given, perhaps as in rickets, we could alleviate the severity of the defects.

Summary and Conclusions. A case of cleido-cranio dysostosis is reported with Roentgen ray and blood chemistry studies. A family tree and brief notes on members of the immediate family are given. The blood phosphorus and blood calcium of these 7 individuals is compared with figures on similar cases given by other writers. The blood chemical findings in the adult members are normal, but the children have a normal calcium with a lowered phosphorus percentage.

Acknowledgment is made to the helpful coöperation of the Department of Radiology in the preparation of the Roentgen ray photographs, and to the Pathological Laboratories for the blood chemical examinations.

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SYMPATHOGONIOMA OF THE ADRENAL.

H. LeBaron Peters, B.A., M.D.,
PATHOLOGIST,

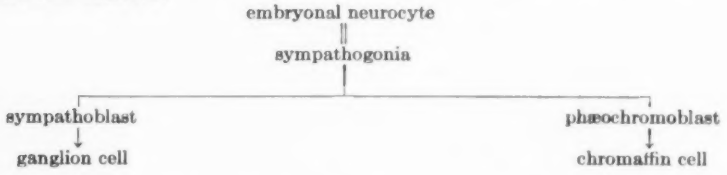
AND

Benjamin Horn, B.S., M.D.,
ASSISTANT PATHOLOGIST, BRIDGEPORT HOSPITAL,
BRIDGEPORT, CONN.

(From the Pathological Laboratory of the Bridgeport Hospital.)

Sympathogonioma of the adrenal gland is a tumor growth originating in the adrenal medulla derived from the primitive cells of the sympathetic nervous system. Marchand, the first to describe an adrenal tumor (1891), suggested that tumors of the adrenal medulla might have their origin in the embryonic sympathetic nerve cells. In 1910, through the work of Wright[1] these tumors were called sympathetic neuroblastomas. Since then, several tumors of this type have been recorded in the literature. That these tumors are very infrequent is evident when we note that Saphir[2] reported his case as the only one in 3950 autopsies. Warthin[3] did not even mention this type of tumor in reporting an analysis of 2000 cases of malignant neoplasms in the young at the University of Michigan. Also, Jacobsen and Hosoi[4] reported only a single case from the Albany Hospital in the last 30 years, while our case is the first on record from this hospital in the last 25 years. In view of the above reports we may say that this type of adrenal tumor is relatively a rare occurrence; and because of the relative infrequency and the interesting features it presents, we add our case to the literature.

In the normal embryonal development of the sympathetic ganglia, the first and most undifferentiated cell arises from the primitive neural canal and is called the embryonal neurocyte. Its development into mature ganglion cells and chromaffin cells may be tabulated as follows:



A tumor arising from the sympathogonia is called a sympathogonioma, while a tumor consisting of sympathoblasts is a sympathoblastoma and a tumor arising from the ganglion cells is a ganglioneuroma. While such a nomenclature is useful in designating

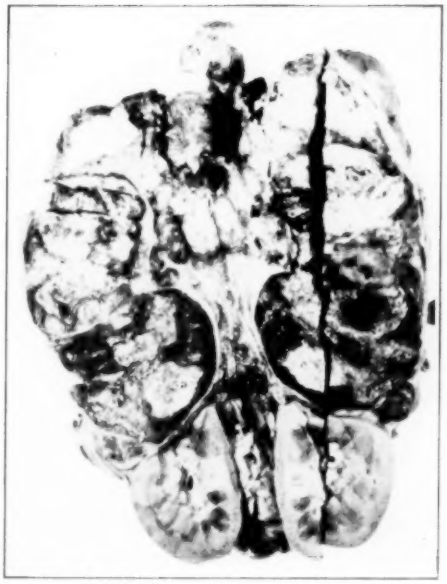


FIG. 1.—Photograph of sympathogonioma of the right adrenal.

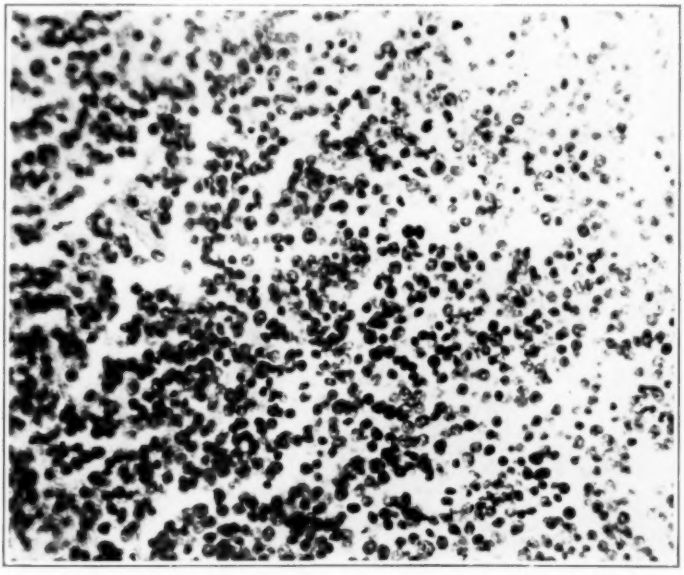


FIG. 2.—Microphotograph of sympathogonioma of adrenal showing the primitive sympathetic nerve cells. Hematoxylin-eosin stain. × 250.

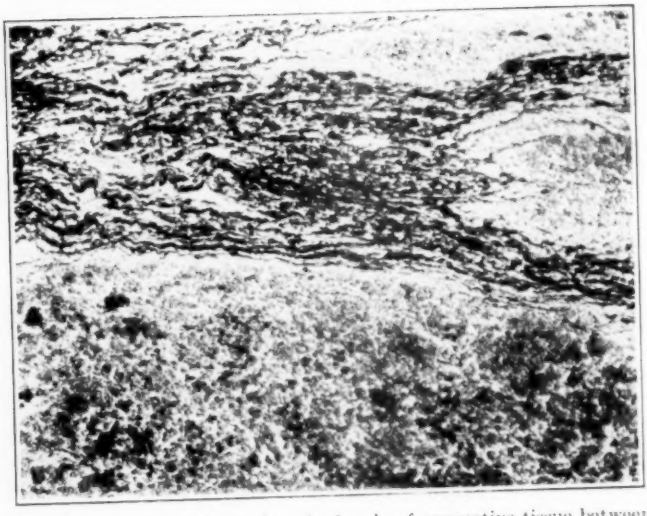


FIG. 3.—Microphotograph showing the bands of connective tissue between areas of densely grouped cells showing complete absence of intercellular stroma. Klarfeld's stain. ×125.

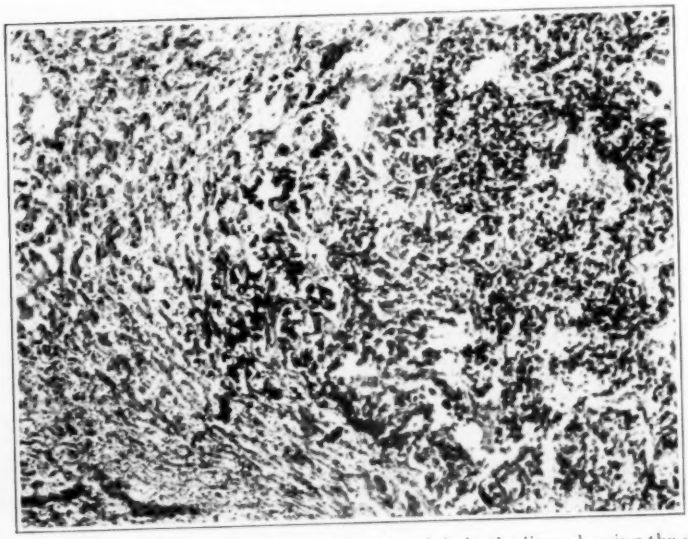


FIG. 4.—Microphotograph of the metastatic nodule in the liver showing the small round cell infiltration and necrosis of the immediate surrounding liver cells. Hematoxylin-eosin stain. ×125.

sympathetic nerve tumors, in reality these growths almost always contain cells of the different stages of development. In the case we are reporting, the tumor showed a predominance of the more immature cells, the sympathogonia, with a very few scattered sympathoblasts. According to the classification proposed by Bielschowsky,[6] we designate our tumor a sympathogonioma. Dr. H. M. Zimmerman of the Yale Medical School has confirmed this diagnosis.

In general sympathogonioma is most common in the newborn and the young but cases have been reported in adults by Ritter,[5] Meltzer,[7] and by Symmers.[8] Being composed of primitive undifferentiated cells, the sympathogonioma is very highly malignant and metastasizes rapidly especially to the liver as was found in our case.

Grossly, the sympathogonioma tumors may or may not be encapsulated and are fairly soft in consistency. They may grow to the size of an apple and on section, the cut surface presents a variegated appearance showing areas of hemorrhage and degeneration. Metastases may appear in the mesenteric and retroperitoneal lymph nodes and bone in addition to the liver. Microscopically, the tumor consists of large numbers of small undifferentiated round cells with oval deeply staining nuclei, rich in chromatin and surrounded by a very delicate ring of cytoplasm. The cells may be arranged diffusely or in alveolar formation. In the metastatic lesions, the structure is composed mainly of small round cells.

Case Reports. D. P. B., a male child, 2 years of age, was admitted to the Pediatric service of Dr. C. V. Calvin on August 11, 1933 for listlessness and swelling of the abdomen. The past history and family history were essentially negative.

The present illness began 3½ weeks previously when the child became listless and developed a slight fever. Under the care of the family physician the child apparently improved for a few days, but again became listless. A few days before admission, the mother noticed that the child was slightly yellow and that the abdomen was getting larger. On admission, examination showed a fairly well-developed and fairly well-nourished white male child moderately pale and quite irritable. There was no general glandular enlargement. The lungs showed dullness on percussion over the right chest posteriorly from the level of the spine down, with diminution of the breath sounds. The heart was normal in size, regular, rapid rate of 140 per minute but no murmurs. The abdomen was markedly distended with prominence of the superficial veins of the skin. The liver appeared to be enlarged, the lower edge being palpated at the level of the umbilicus. There was a feeling of fullness on palpation in the right costovertebral area but no tenderness could be elicited. The extremities showed a slight edema from the toes up to the knees.

Course During Illness. The patient slept most of the time and when awake he was irritable, restless and refused to eat. The abdomen gradually increased in size with the accumulation of fluid. Because of the enlarged abdomen with ascites developing fairly acutely, an exploratory laparotomy was performed on August 19, through an upper right rectus incision and when the peritoneal cavity was opened, a great amount of straw-colored fluid escaped from the wound. The liver was found to be moderately enlarged but smooth. As the condition of the patient was critical, extensive exploration was not possible. The patient gradually became weaker and

soon after regaining consciousness from the anesthesia lapsed into coma and died the next day.

The temperature varied between 98° and 103°, the pulse between 110 and 160, and respirations around 36 per minute. Mantoux tests with 0.1 mg. and 1 mg. of old tuberculin were negative. Blood examination on August 11 showed R. B. C. 3,300,000, W. B. C. 6825 with Poly. 76%—Band forms 17%, S. L. 20%, Mono. 4%, Eos. 2%. Hemoglobin 52 (Sahli). Platelets 464,000. Icteric index 10. Another blood count 5 days later was essentially the same. Bleeding time 2 min. Venous coagulation time 5½ min. with clot retraction at 15 min. Blood Wassermann and Kahn tests were negative. Sedimentation time was 1 hr. and 25 min. Blood cultures showed no growth. The urine on repeated examinations showed a very faint trace of albumin. Roentgenologic examination on August 12 reported that the right dome of the diaphragm was elevated, the result of an enlarged liver.

Necropsy (restricted to the operative incision, done 1 hr. after death). On opening the incision a quart of blood-tinged fluid issued forth. The right dome of the diaphragm was at the level of the third rib in the midclavicular line, the left dome at the fourth intercostal space. The lower border of the liver extended 4 inches below the costal margin, was pale yellow and smooth, except for 2 very small white nodules about 1 cm. in diameter on the superior surface of the right lobe. The abdominal viscera appeared to be pushed forward by some mass deeper in the abdominal cavity. There were numerous small glands at the root of the mesentery, varying in size from 1 to 5 cm. in length, pale red and very soft in consistency. The spleen appeared to be normal. The liver when removed was enlarged, weighing 480 gm., capsule smooth and pale and except for the two small nodules on the superior surface showed no gross change. The left kidney was normal in size, pale red in color and weighed 68 gm. The left adrenal was normal in size and the cut surface showed no gross change. The right kidney was found to be compressed at the upper pole by a mass which replaced the right adrenal gland (Fig. 1). The mass measured 6 inches long, 4½ inches wide and 4 inches in depth. It was grossly nodular in appearance, grayish-yellow in color, and moderately soft in consistency. Attached to the posterior surface were numerous matted glands. On section, the cut surface of the tumor mass presented a variegated appearance consisting of reddish-yellow areas with parts showing hemorrhage and necrosis. Near the periphery, in some sections, could be seen portions of the yellow-brown structure of the adrenal cortex. The compressed kidney below the tumor mass showed no neoplastic involvement.

Sections of the tumor were stained with hematoxylin and eosin, Van Gieson's stain, Mallory connective tissue stain, Klarfield's tannic acid silver carbonate stain and with Bielschowsky stain. Histological examination of the various sections showed that the tumor consisted mainly of small round cells about the size of small lymphocytes, with round deeply staining stippled nuclei and surrounded by very scant cytoplasm hardly discernible (Fig. 2). These cells are identical with the cells described by Bielschowsky as sympathogonia.

Scattered among these cells were seen some somewhat larger round cells with clearer vesicular nuclei. In the main, the tumor cells had no definite arrangement, lying diffusely in a very small amount of connective tissue stroma. Although the neoplasm had very little intercellular stroma, there were seen rather wide bands of connective tissue which subdivided it into zones of polygonal shape and various sizes. These bands were best seen in the Klarfield's tannic acid silver carbonate stain (Fig. 3).

Bielschowsky preparations for axis cylinders did not reveal any such structures in the neoplasm. Nissl preparations to demonstrate tigroid

substance in the cytoplasm were also negative. These results indicated that this neoplasm was a very primitive one and the cells represented sympathogonia.

Histologic examination of the small nodule in the liver showed a small round cell infiltration with necrosis of the immediate surrounding liver cells (Fig. 4).

Summary. 1. Sympathogonioma of the adrenal gland is a rare tumor, consisting of the most primitive sympathetic nerve cells (sympathogonia).

2. A case of sympathogonioma of the adrenal is reported in a child aged 2 years with metastases in the liver and retroperitoneal lymph nodes, fatal within 5 weeks after the onset of illness.

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THE TREATMENT OF BICHLORID OF MERCURY POISONING: A STUDY OF 46 CASES.

By William B. Porter, M.D.,
PROFESSOR OF MEDICINE AND CHIEF OF MEDICAL SERVICE,
AND
C. E. Simons, M.D.,
RESIDENT PHYSICIAN IN MEDICINE, MEDICAL COLLEGE OF VIRGINIA,
RICHMOND, VA.

(From the Hospital Division, Medical College of Virginia.)

This study is concerned with an analysis of 46 patients who gave conclusive histories of having taken orally corrosive sublimate and who were treated on the medical wards of this hospital from January 1, 1927 to December 31, 1933. Eleven additional patients seen during this period gave similar histories, but the subsequent data and their clinical behavior introduced reasonable doubt as to the accuracy of their statements and they were therefore discarded from this study.

The evaluation of any method of therapy in corrosive sublimate poisoning must be made with the full realization that there are concerned many factors which cannot be completely and adequately subjected to analysis. Comparative results are therefore not entirely trustworthy, yet the number of cases here studied is sufficient more

or less to eliminate the variable equations and the results obtained do indicate that the therapy adopted is superior in kind.

All of the patients were observed for a length of time sufficient for the ultimate outcome to be noted. There were only 3 deaths, a mortality of 6.5%.

The therapy was designed in the full realization that for the present there is not available a trustworthy antidote for mercury poisoning. In the light of this important fact we based our therapeutic technique upon the known effects of ingested mercury and the probable pathogenesis of the fatal sequelæ.

The corrosive effect of bichlorid of mercury on the gastro-intestinal tract initiates a physical and biochemical state similar in its essential nature to that seen in extensive cutaneous burns. At times the shock and circulatory depression is so severe that death occurs within a few hours; and while this is unusual, the development of renal insufficiency immediately after the taking of the mercury frequently occurs. One of our patients excreted no urine for 192 hr., the anuria having followed immediately the taking of the mercury. Recovery occurred despite the fact that a blood creatinin of 12.2 mg. per 100 cc. was reached before diuresis was established.

The renal insufficiency follows immediately upon ingestion of mercury in those patients who have taken large amounts of the substance and in whom the corrosive effects are severe. It is undoubtedly due in part to the direct action of mercury on the capillaries of the glomeruli, but is more largely due to the concentration of blood and the depletion of the electrolytes operating jointly with disturbance of blood flow induced by shock and possibly more specifically through the mechanism of the vasomotor innervation to the splanchnic and renal vessels.

After the first 24 hr., renal insufficiency is the most important complication and it is related directly to the lesions produced in the kidney by the absorbed mercury. These lesions consist mainly of extensive necrosis of the epithelial cells lining the convoluted tubules and the proximate convoluted segments are those most severely involved. The glomeruli appear normal except for varying degrees of congestion and occasional swelling and desquamation of the capsular epithelium. One finds a reasonable explanation for the escape of the glomeruli on the one hand and the severe necrosis of the tubular epithelia on the other in the high concentration of the glomerulus filtrate which occurs in the convoluted tubules. It is certain that mercury is excreted by the glomeruli and is dealt with by the tubules in the same fashion as other non-threshold bodies, and therefore reaches a high concentration in this area. Cushny[1] states that 1 liter of urine is formed from 63 liters of glomerulus filtrate and it is reasonable to assume that a much higher concentration exists in mercury poisoning where dehydration occurs rapidly and is at times severe. Fatal uremia appears during the "gray" stage of

mercury nephrosis in the large majority of those who succumb to uremia after the first 48 hr. During this period the necrotic cells are being crowded into the lumen of the urinary tubules by the rapid development of new epithelia. Mechanical blockage of tubules by cell débris and urinary casts conceivably could cause complete cessation of filtration by these glomeruli. The absence of dilatation of the glomeruli has been suggested as an argument against the obstructive mechanism of the uremia of mercury nephrosis. This objection does not appear reasonable in a condition so acute, and furthermore it is not tenable that dilatation could occur when the kidney, as the result of the diffuse pathologic processes, is tensely swollen in its capsule. If then renal insufficiency is caused by the effects upon the glomeruli of the mechanically obstructed convoluted tubules, it follows that consideration must be given to the use of measures which may prevent this complication.

The exact mechanism of the formation of urinary casts is not understood, yet it is known that they are composed of precipitated protein and varying amounts of epithelial cell débris. Meyler[2] believes that urinary acidity reduces the globulin fraction to its isoelectric point and that the precipitation of this protein forms casts. Whether or not this be entirely correct, it is nevertheless true that blood and tissue proteins are less soluble in acid urine which has a pH of approximately 5 than in urine alkalin to litmus which has a pH of approximately 7.8. The isoelectric points of serum albumin and serum globulin are pH 4.7 and pH 5.7 respectively. Their place of least solubility is around the average urinary acidity. These facts have suggested a reasonable basis for the forcing of fluids to increase the amount of glomerulus filtrate in an effort to prevent stasis; and for the use of sodium bicarbonate to maintain urine alkalin to litmus at the kidney level, and conceivably to modify cast formation in the urinary tubules.

In the early stages of poisoning there occurs blood concentration and a definite reduction of the electrolytes as indicated by the plasma chlorids.

In all of the patients of this series with a leukocyte count above 20,000 per c.mm. the red cell count was 5,000,000 or more per c.mm. In this same group the patients on whom plasma chlorid studies were made all were below normal, the lowest being 186 mg. per 100 cc.; the highest 420 (as sodium chlorid). These findings indicate the necessity for using a solution for the relief of dehydration and for the replacement of plasma electrolytes.

The colon is an important avenue for the elimination of mercury, and colitis occurring in mercury poisoning is due to the action of mercury on the epithelial lining of the gut, during the process of excretion. It is improbable that colitis can be prevented by colonic irrigation, yet it is conceivable that irrigations may prevent reabsorption of excreted mercury.

Chart I.—Bichlorid of Mercury Poisoning.

Analysis of patients having leukocytosis below 20,000—no deaths.

Race.	Sex.	Age.	HgCl$_2$ grains.	Time taken.	Time of vomiting.	Time of lavage.	Pharyngitis.	Epigastric burning.	Diarrhea.	Stomatitis.	White blood count (in thousands).	Urinalysis.					Blood chemistry.			Associated disease.	Accidental.	Suicidal.	Recovered.
												Albumen.	Red blood cells.	White blood cells.	Casts, hyalin.	Casts, granular.	N. P. N.	Creatinin.	Plasma chlorids.				
W	F	20	45	9.15 P.M.	9.25 P.M.	10.00 P.M.	+	+	0	0	11.6	Tr.	0c	0c	+	+	34	?	?	0	Yes	No	Yes
W	F	21	6	10.00 P.M.	10.30 P.M.	11.15 P.M.	+	+	0	0	7.4	Tr.	0c	0c	0	0	42	?	?	0	0	Yes	Yes
W	M	23	19	6.00 P.M.	0	7.15 P.M.	+	+	0	0	10.9	Tr.	0	0	0	0	39	?	424	0	0	Yes	Yes
W	F	28	6	5.00 P.M.	5.10 P.M.	6.00 P.M.	0	0	0	0	9.0	0	0	0	0	0	26	?	?	0	0	Yes	Yes
W	F	20	15	11.50 P.M.	0	12.25 A.M.	+	2+	0	0	16.0	Tr.	+	0c	0	0	34	?	460	0	0	Yes	Yes
W	F	18	7.3	8.30 P.M.	8.40 P.M.	9.00 P.M.	0	2+	0	0	12.0	Tr.	0c	0	0c	0c	29	?	?	0	0	Yes	Yes
W	F	25	9	2.30 P.M.	0	3.00 P.M.	4+	2+	0	+	14.5	Tr.	0c	0c	0	0	30	?	?	0	0	Yes	Yes
W	M	26	15	11.00 P.M.	0	11.45 P.M.	0	0	0	0	7.2	0	0	0	0	0	36	?	?	0	0	Yes	Yes
W	M	37	22	9.30 A.M.	10.45 A.M.	11.00 A.M.	4+	3+	0	+	15.0	Tr.	0c	0c	0	0c	34	?	?	0	0	Yes	Yes
W	M	39	15	2.30 P.M.	0	3.15 P.M.	+	+	0	+	17.0	0	0c	0	0	0	38	?	?	0	0	Yes	Yes
W	M	28	7.3	1.00 P.M.	1.10 P.M.	1.40 P.M.	0	+	0	0	13.0	0	0	0	0	0	33	?	?	0	Yes	No	Yes
W	F	20	3	7.30 P.M.	0	8.15 P.M.	+	+	0	0	10.8	0	0	0	0	0	29	?	?	0	Yes	No	Yes
W	M	41	20	6.00 P.M.	6.15 P.M.	6.30 P.M.	+	+	0	+	16.6	Tr.	0c	0	0	0	42	?	?	0	0	No	Yes
C	F	33	15	12.00 M.	12.15 A.M.	1.30 A.M.	2+	2+	+	+	15.9	3+	+	0c	0c	2+	34 (76) 38	?	388	0	0	Yes	Yes
C	F	34	7.5	9.00 P.M.	9.10 P.M.	9.30 P.M.	+	+	0	0	10.8	0	0	0	0	0	32	?	?	0	0	Yes	Yes
W	M	22	7.3	6.00 P.M.	6.20 P.M.	6.45 P.M.	+	+	0	0	12.4	+	0c	0	0c	0	?	?	?	0	0	Yes	Yes
W	M	25	15	1.15 A.M.	1.30 A.M.	2.15 A.M.	0	+	0	0	6.8	0	0	0	0	0	38	?	?	0	0	Yes	Yes
W	M	20	6	12.30 A.M.	0	1.30 A.M.	+	+	0	0	7.3	0	0	0	0	0	28	?	?	0	0	Yes	Yes
W	M	43	3.5	9.30 A.M.	0	10.15 A.M.	0	0	0	0	6.8	0	0	0	0	0	34	?	?	0	0	Yes	Yes
W	M	19	35	6.30 A.M.	6.15 A.M.	7.15 A.M.	0	+	0	0	7.4	Tr.	0c	0	0	0	32	?	?	0	0	Yes	Yes
W	M	43	7.3	9.00 P.M.	0	10.00 P.M.	+	+	0	0	4.2	Tr.	0	0	0	0	44	?	?	Pern. anem.	0	Yes	Yes
W	F	30	8.2	4.15 P.M.	0	4.40 P.M.	+	+	0	+	10.4	Tr.	0c	0	0	0	39	?	?	0	0	Yes	Yes
W	F	23	7.3 In sol.	4.00 P.M.	0	4.30 P.M.	+	+	0	0	9.6	0	0	0	0	0	38	?	?	0	Yes	No	Yes
W	F	22	20	4.00 P.M.	0	4.30 P.M.	0	+	0	+	12.0	Tr.	0c	0	0	0	38	?	?	Pregnancy	0	Yes	Yes
W	F	33	5	?	0	30 min. later	+	+	0	0	8.6	0	0	0	0	0	30	?	?	0	0	Yes	Yes
W	F	29	11	3.00 P.M.	3.15 P.M.	3.30 P.M.	+	+	0	+	12.3	0	0	0	0	0	32	?	?	0	0	Yes	Yes
W	F	16	7.3	?	0	35 min. later	+	+	0	0	7.6	0	0	0	0	0	38	?	?	0	0	Yes	Yes
W	M	25	7.3	?	Immediately	15 min. later	+	+	0	0	9.0	0	0	0	0	0	38	?	?	0	0	Yes	Yes
W	F	19	7.3	10.00 A.M.	10.10 A.M.	10.20 A.M.	2+	+	0	0	8.4	0	0c	0	0	0	36	?	?	0	0	Yes	Yes
W	M	26	15	8.00 P.M.	8.15 P.M.	8.30 P.M.	+	+	0	0	11.8	Tr.	0c	0	0	+	34	?	?	0	0	Yes	Yes
W	F	18	15	10.30 P.M.	?	11.00 P.M.	+	+	0	+	12.4	Tr.	0	0	0	0c	24	?	?	0	0	Yes	Yes
W	F	23	?	?	?	20 min. later	0	0	0	0	6.8	0	0	0	0	0	?	?	?	0	0	Yes	Yes

Chart II.—Analysis of a Series of Cases of Bichlorid of Mer

Chart II.—Analysis of a Series of Cases of Bichlorid of Mercury Poisoning.

Race.	Sex.	Age.	HgCl$_2$, grains.	Time taken.	Time of vomiting.	Time of lavage.	Pharyngitis.	Epigastric burning.	Diarrhea.	Stomatitis.	White blood count (in thousands).	Urinalysis: Albumen	Urinalysis: Red blood cells	Urinalysis: White blood cells	Urinalysis: Casts, hyalin	Urinalysis: Casts, granular.	Blood chemistry: N P N.	Blood chemistry: Creatinin	Blood chemistry: Plasma chlorids	Associated disease.	Accidental	Suicidal.	Recovered	Died.	Remarks.
ANALYSIS OF FATAL CASES.																									
W	M	34	45	7.00 P.M.	7.00 to 10.00 P.M.	8.30 P.M.	4+	4+	4+	3+	42.0	2+	2+	0c	2+	2+	40 to 312	2.1 to 18.4	368 to 189	0	0	Yes	No	Yes	Death on 16th day; uremia and colitis.
W	F	18	40	11.15 P.M.	?	12 hr. later	2+	2+	+	2+	52.0	2+	+	0	0	0	126	8.4	?	0	0	Yes	No	Yes	Death in 56 hr.; shock and uremia.
W	M	42	15	?	?	20 hr. later	+	+	3+	+	39.0	2+	+	+	+	2+	72 to 384	6.4 to 21.0	?	0	0	Yes	No	Yes	Death on 9th day; uremia and colitis.
ANALYSIS OF PATIENTS HAVING LEUKOCYTOSIS ABOVE 20,000 WITH RECOVERY.																									
W	F	23	11	6.15 P.M.	6.45 P.M.	8.00 P.M.	0	2+	0	+	20.1	Tr.	+	0c	0	0	42	?	?	0	0	Yes	Yes	No	
W	M	31	9	1.00 P.M.	1.30 P.M.	2.00 P.M.	+	2+	0	0	21.4	Tr.	0c	0c	+	2+	40 / 24	?	386	0	0	Yes	Yes	No	
W	F	27	22	12.30 A.M.	?	2.00 A.M.	3+	3+	0	+	24.6	+	+	0c	+	+	32 / 46	?	378 / 420	0	0	Yes	Yes	No	
W	M	26	37	7.00 P.M.	7.15 P.M.	27 hr. later	4+	4+	0	4+	26.0	2+	+	0c	+	+	62 / 160 / 126	4.4 / 12.2 / 1.4	312 / 384	0	0	Yes	Yes	No	
W	M	48	25	11.30 A.M.	0	12.00 M.	+	2+	0	0	24.0	+	0c	0	0	0	44	?	310	Pul. tb.	0	Yes	Yes	No	
W	M	44	17	9.30 P.M.	9.45	10.30 P.M.	+	2+	0	+	20.6	Tr.	+	0c	0	0c	26	?	?	0	0	Yes	Yes	No	
W	M	27	5	2.00 P.M.	2.15 P.M.	3.10 P.M.	+	+	0	+	20.4	2+	0c	4+	0c	+	64	?	?	0	0	Yes	Yes	No	
W	F	36	20	12.30 A.M.	?	2.30 A.M.	2+	2+	+	2+	26.0	+	+	+	+	+	39 / 26 / 64 / 228	..	388	"GC"	0	Yes	Yes	No	
W	M	21	22	8.30 P.M.	8.40 P.M.	10.00 P.M.	+	2+	0	+	36.2	+	0c	0	0	0c	34	?	?	0	0	Yes	Yes	No	Alkali begun on 10th day.
W	M	19	73 In sol.	3.00 A.M.	3.15 A.M.	3.40 A.M.	+	+	0	0	21.0	Tr.	0	0	0	0	92	?	?	0	Yes	No	Yes	No	
W	F	20	30	3.00 P.M.	3.10 P.M.	9.30 P.M.	+	2+	0	+	26.8	Tr.	0c	0	0	0	38 / 100 / 28	4.2 / 1.4	?	0	0	Yes	Yes	No	

Three (3) deaths in 14 cases with a leukocyte count above 20,000. Percentage deaths, 21·43 per cent.

Obviously the prompt and thorough removal of the mercury from the stomach by gastric lavage is the most important procedure in reducing morbidity and mortality. For the lavage a saturated solution of sodium bicarbonate is used, the reason for this being that the albuminates formed from contact of the mercury with the gastric mucosa, ingested proteins and mucin are readily soluble in an alkalin solution and will consequently be more completely removed.

The outline of therapy which follows is that used routinely on the medical wards and in principle has been adhered to in every instance in the treatment of this series of cases of mercury poisoning. Any modification in details of treatment has been influenced by variations from the expected clinical course of patients and to the development of unusual complications.

CHART III.—SUMMARY OF RESULTS.

	White.		Negro.	
	Male.	Female.	Male.	Female.
Oldest	48 yrs.	36 yrs.	..	34 yrs.
Youngest	19 yrs.	16 yrs.	..	22 yrs.
Average age	29 yrs.	24 yrs.	..	28 yrs.
Number of cases	22	22	..	2
Deaths	2	1	..	0

Total number of cases, 46; total number of deaths, 3 (6.5%).

	Plasma non-protein nitrogen.		Colitis and uremia.	Salivation and alveolar necrosis.	Leukocyte count.	
	Above 50 mg.%.	Below 50 mg.%.			Above 20,000.	Below 20,000.
Number of cases	9.0	37.0	5.0	2.0	14.0	32.0
Per cent of cases	19.5	80.5	10.8	4.3	30.4	69.6
Deaths	3.0	0.0	3.0	0.0	3.0	0.0

Treatment in Detail. 1. Immediate gastric lavage with a saturated solution of sodium bicarbonate, temperature 100° F. This is continued until the return fluid *is clear*. The lavage is repeated every 12 hr. for the first 5 days and is continued over a longer period if the chemical analysis of the washings shows mercury.

2. Morphin sulphate is administered immediately after the primary gastric lavage. This is repeated at intervals dependent upon the degree of shock, vomiting and pain; but the principle should be to relieve discomfort, retching and shock.

3. Sodium bicarbonate, 500 cc. of a 5% solution, is given intravenously immediately after the lavage, and 1000 cc. of normal saline solution are administered subcutaneously. As long as vomiting persists the same amount of each solution is repeated every 12 hr.

4. Sodium bicarbonate 5 gm. is given orally every 3 hr. during the day and every 4 hr. during the night. The amount of bicarbonate may be varied provided the urine is kept alkalin to litmus.

5. The total daily fluid intake must be at least 5000 cc. for an adult, and this amount must be maintained by oral, subcutaneous or intravenous

route, dependent upon the ability of the patient to retain the substances taken orally. Preference is always given the oral method.

6. The daily diet is orange juice 500 cc., milk 1000 cc. and beta lactose 100 gm. One egg daily is added as soon as vomiting is controlled. The feedings should be given every 3 hr. If vomiting interrupts the feeding schedule, 10% glucose solution is given intravenously in amounts sufficient to maintain an intake of at least 1000 calories. The bicarbonate solution can be made with the glucose solution and the injection given by the intravenous "drip" method. After the first week adequate nutrition and medication are in some cases interrupted by the development of a severe stomatitis and esophagitis. In 2 of the patients of this series a gastrostomy was done and we feel that it was the deciding factor in recovery. All the food and medicine were given through the gastrostomy tube and only water was given orally.

7. A colonic irrigation, using 5% sodium bicarbonate solution is given daily and is continued until recovery is assured.

Discussion. In evaluating a therapeutic principle, conservatism guided by a critical assay of the variable actors is imperative lest credit be given where credit is not due. To conclude that alkalization is solely responsible for the results obtained in this series of cases would be but to add another to those errors which arise in the evaluation of therapeutic procedures. Manifestly early emesis, the presence of food in the stomach, and prompt and thorough gastric lavage were largely responsible for the low mortality and morbidity.

An analysis of the methods of treatment advocated by various writers shows in common the principle of elimination and the use of various substances which tend to promote alkalinization. Evans[3] in 1880 advocated alkalies in the treatment of mercury poisoning and Hirsch[4] suggested sodium bicarbonate as an antidote for mercury. Weis[5] emphasized the importance of alkalies and recommended sodium bicarbonate for gastric lavage. He based his therapy on the observations of MacNider[6] which indicated that an "acid intoxication" was an important feature of bichlorid of mercury poisoning. However, when one reviews the various methods of treatment advocated he feels that there is little justification for their complexity. The efficiency of any therapy for a disease caused by the ingestion of a poisonous substance must rest primarily upon an efficient method for the prompt removal of the harmful material from the stomach. The method must be simple, the drugs used in the treatment easily obtainable, and in the absence of a known antidote the therapeutic technique must be designed so that the fatal sequelæ may be prevented. The measures used in the treatment of this series of cases seemingly met these requirements quite satisfactorily.

An analysis of Chart II shows that of the 11 patients with a leukocyte count above 20,000 per c.mm. who recovered, only 1 had symptoms indicating colitis and that of mild type and short duration. Only 4 had a plasma non-protein nitrogen as high as 50 mg.

per 100 cc. These data suggest that the therapy used modified or prevented the development of the kidney lesions responsible for renal insufficiency; and almost totally eliminated colitis.

The infrequent occurrence of true mercury stomatitis was especially striking. Stomatitis occurring immediately as a result of the corrosive effects of mercury was present in 15 patients, but only 2 patients developed the severe type with salivation and alveolar necrosis. It is interesting that both of these patients developed anuria immediately after taking mercury. In one of them anuria lasted 192 hr., and in the other 84 hr. Both patients recovered, although the stomatitis was complicated by severe esophagitis which necessitated gastrostomy.

The prognostic significance of the leukocyte count is emphasized by this series of cases. The 3 fatal cases had leukocyte counts above 35,000 per c.mm., and only 1 patient with a leukocyte count above 30,000 per c.mm. recovered.

Conclusions. 1. While there is no known specific antidote for corrosive sublimate poisoning, yet a therapeutic scheme which emphasizes the use of sodium bicarbonate solution for gastric lavage, for colonic irrigation, and for dosage in amounts sufficient to maintain urine alkalin to litmus apparently reduced the mortality and morbidity in this series of patients so treated.

2. A concept of the mechanism of renal insufficiency in mercury nephrosis is presented and a tenable explanation of the mode of action of alkalization in preventing uremia is offered.

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A STUDY OF AURICULAR FIBRILLATION FOLLOWING OPERATIONS FOR GOITER.

By A. Carlton Ernstene, M.D.,

and

Bert E. Mulvey, M.D.,

Cleveland Clinic, Cleveland, Ohio.

Auricular fibrillation is the most common cardiac irregularity observed in hyperthyroidism. In a considerable number of cases the arrhythmia first develops shortly after thyroidectomy, and it is with this postoperative complication that the present investigation

is concerned. The study is based on 405 consecutive cases in which thyroidectomy was performed. Of these patients, 192 had adenomatous goiter without clinical or laboratory evidence of hyperthyroidism, while the remaining 213 had hyperplastic or adenomatous goiter with hyperthyroidism. Sixteen patients with hyperthyroidism had auricular fibrillation before operation (7%). The arrhythmia also was present before operation in 2 individuals who had adenomatous goiter without hyperthyroidism. Auricular fibrillation developed after operation in 35 of the 387 patients who had regular rhythm during the pre-operative period. It seemed that analysis of these 35 cases might yield considerable information concerning the pathogenesis and clinical importance of postoperative auricular fibrillation.

Of the 35 patients 31 had hyperthyroidism. They constitute 16% of the 197 patients with thyrotoxicosis who had normal rhythm before operation. The other 4 individuals presented no evidence of hyperthyroidism. Of the 35 patients 27 were women and 9 were men. All were between the ages of 35 and 61 years, but only 5 were less than 40. The basal metabolic rates in the patients with hyperthyroidism ranged from +8 to +76%. In 11 individuals the rate was +20% or less, but 5 of these had received iodids or Lugol's solution before entrance to the hospital. The metabolic rates in the patients without hyperthyroidism were between −8 and +9%. In the patients with hyperthyroidism, symptoms had been present for 4 months to 8 years, with an average duration of 23 months. Nine patients had had symptoms for more than 30 months; 1 had had a thyroidectomy for hyperthyroidism 8 years before the present admission and had had a gradual recurrence of symptoms after 4 years. Of the 35 patients, the 27 who were able to estimate the duration of the thyroid enlargement had had it from 1 to more than 40 years. Only 3 of the 27, however, had had noticeable goiter for less than 5 years.

Palpitation and dyspnea on exertion had been noted by practically all of the patients, but none had had myocardial failure and none presented evidence of congestion in the pulmonary or peripheral circulation at the time of admission to the hospital. The clinical histories suggested that 2 of the patients with hyperthyroidism had had short paroxysms of auricular fibrillation in the past. Two patients had had rheumatic fever during adolescence, and 3 others had had frequent attacks of tonsillitis. In 5 patients, all with hyperthyroidism, the systolic blood pressure remained above 150 mm. and the diastolic pressure above 90 mm. throughout the period of observation. Several individuals had slight or moderate degrees of peripheral arteriosclerosis, but extreme sclerosis was not recorded in any instance. Slight enlargement of the heart, as estimated by physical examination and roentgenologic studies, was present in 4 patients. Seventeen had systolic murmurs over the cardiac apex

or pulmonic valve area, and in 3 of these there was a systolic murmur in the right second intercostal space. None had a diastolic murmur. One patient with hyperthyroidism had numerous premature beats during the pre-operative period. Electrocardiograms were made in approximately one-half of the cases. Slight or moderate degrees of left-axis deviation were observed occasionally, but the tracings usually were essentially normal. Krumbhaar,[1] however, observed either right or left axis deviation to be frequent in patients with hyperthyroidism.

Onset of Postoperative Auricular Fibrillation.—In 2 individuals, auricular fibrillation developed during the operation, and in 4 others it appeared within the first 23 hours after operation. In 23 of the 35 patients, the irregularity began between 24 and 59 hours after operation, while in 6 it developed between 60 and 120 hours after operation.

In all patients, auricular fibrillation appeared during a time when the temperature was elevated, and in a few, normal rhythm was reëstablished as the temperature curve returned rapidly to normal. A number of patients, however, had only slight postoperative fever, and in a majority it was not possible to establish a relation between the course of the temperature curve and the duration of the arrhythmia.

In 3 patients in whom the irregularity developed during the first 23 hours after operation, normal rhythm was reëstablished after 3 to 13 hours, only to be followed by a second paroxysm of fibrillation 20 to 46 hours later.

Duration of Postoperative Auricular Fibrillation.—The arrhythmia lasted for less than 24 hours in 18 of the 35 patients and in only 8 individuals did it persist for more than 48 hours. The longest duration observed was 8 days.

Symptoms. Several patients complained of palpitation during the period of fibrillation, and in 4, slight or moderate dyspnea also was noted. In 1 individual, whose arrhythmia lasted 74 hours, râles developed over the bases of the lungs and moderate edema appeared over the lower back.

Type of Goiter. Pathologic examination of the surgical specimens from the 213 patients with hyperthyroidism revealed hyperplastic goiter in 117 instances, combined hyperplastic and adenomatous goiter in 17, colloid goiter with multiple adenomata in 62, colloid goiter in 9 and adenomatous goiter in 8. In the 31 individuals with hyperthyroidism in whom auricular fibrillation developed after operation, the specimen revealed hyperplastic goiter in 9 instances, hyperplastic and adenomatous goiter in 2, colloid goiter with multiple adenomata in 18, colloid goiter in 1 and adenomatous goiter in 1. In all 4 cases in which postoperative fibrillation developed in patients without hyperthyroidism, pathologic examination showed colloid goiter with multiple adenomata.

Discussion. Comparison of the patients who had postoperative auricular fibrillation with those in whom the cardiac rhythm remained regular revealed no differences that might have been used to forecast the development of auricular fibrillation after operation. Studies by several investigators[2,3] have demonstrated that the incidence of auricular fibrillation during hyperthyroidism is more directly related to the age of the patient than to any other measurable factor. The arrhythmia is observed infrequently in thyrotoxic individuals less than 40 years of age. The duration of clinical hyperthyroidism is a less important contributory cause and the degree of elevation of the basal metabolic rate is of little significance.[2,4] The results of the present study indicate that the factors which predispose to the development of postoperative auricular fibrillation are the same as those that govern the occurrence of the arrhythmia in hyperthyroidism before operation. In postoperative auricular fibrillation, however, an additional stimulus connected with the operation or the early postoperative course is necessary to initiate the arrhythmia.

Segall and Means[5] demonstrated that the metabolic rate is increased to a variable but usually considerable degree during the first few days after subtotal thyroidectomy in patients with hyperthyroidism. They believe that the rise is to be explained largely as the result of fever and emotion. It is probable that this increased rate of metabolism and the consequent increased load upon the heart are the essential factors responsible for the initiation of postoperative auricular fibrillation. The same factors may also control the duration of the arrhythmia. It must be emphasized, however, that the irregularity may occur in individuals in whom the postoperative reaction and elevation in temperature are of mild degree.

Postoperative auricular fibrillation is more common both relatively and absolutely in patients with adenomatous goiter than in those with hyperplastic goiter.[4] This cannot be accounted for entirely by differences in the ages of individuals belonging to the two groups. In the present series, 41 patients with hyperplastic goiter and normal rhythm before operation were 45 years of age or more. Of this number, 5 had postoperative auricular fibrillation, an incidence of 12%. Thirty patients with hyperthyroidism, colloid goiter with multiple adenomata and normal rhythm before operation were 45 years of age or more. Postoperative auricular fibrillation occurred in 11 of these, an incidence of 37%. The long duration of thyroid enlargement in the majority of patients with adenomatous goiter suggests an explanation for the more common occurrence of postoperative fibrillation in this group. It is possible that many of these patients have experienced repeated or prolonged periods of low-grade, unrecognized hyperthyroidism before the appearance of symptoms of sufficient severity to necessitate seeking medical advice. Such subclinical thyrotoxicosis might favor the

gradual development of myocardial damage and thus predispose to the development of postoperative auricular fibrillation.

The occurrence of auricular fibrillation after thyroidectomy in 4 patients with no symptoms or signs of hyperthyroidism is of considerable interest. Means[6] recently has emphasized the diagnostic value of observing the effect of iodin on the basal metabolic rate of individuals with obscure hyperthyroidism. It would have been desirable to have made such studies in these patients, for otherwise the possibility of masked thyrotoxicosis cannot be excluded absolutely.

The development of auricular fibrillation after operations for goiter generally is a complication of but little clinical importance. The irregularity usually lasts for less than 48 hours and rarely causes circulatory embarrassment. Normal sinus rhythm almost always is reëstablished spontaneously. In all but a few cases, no treatment is necessary. It has been our practice, however, to begin gradual digitalization with the onset of the arrhythmia so that the complete effect of the drug can be obtained more readily in the rare instances in which mild congestive failure does develop. If the arrhythmia should persist for more than 1 week, quinidin may be used to restore normal rhythm.

Summary and Conclusions. 1. Sixteen (7%) of 213 patients with hyperthyroidism had auricular fibrillation during the pre-operative period; while postoperative auricular fibrillation developed in 31 (16%) of the 197 who had normal rhythm before operation. The arrhythmia was present before operation in 2 of 192 individuals who had adenomatous goiter without hyperthyroidism and developed after operation in 4 other patients in this group.

2. The age of the patient, type of goiter and duration of hyperthyroidism appear to be the most important factors predisposing to the development of postoperative auricular fibrillation. The degree of elevation of the basal metabolic rate is of little significance. The immediate increase in the rate of metabolism following operation probably is the essential factor responsible for the initiation of the arrhythmia.

3. Postoperative auricular fibrillation is more common in thyrotoxic patients with adenomatous goiter than in those with hyperplastic goiter. This difference cannot be explained entirely by differences in the ages of individuals belonging to the two groups. The long duration of thyroid enlargement in the majority of patients with adenomatous goiter may favor the gradual development of myocardial damage, possibly as the result of repeated or prolonged periods of low-grade, unrecognized hyperthyroidism.

4. Postoperative auricular fibrillation generally begins during the first 60 hours after operation. It rarely causes circulatory embarrassment, and normal rhythm usually is reëstablished spontaneously within 48 hours.

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THE ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY INJURIES OF VARIOUS PARTS OF THE VENTRICLES.*

By Herman Korey, B.S.
STUDENT ASSISTANT,
AND
Louis N. Katz, M.D.,
PHYSIOLOGIST AND DIRECTOR OF CARDIOVASCULAR RESEARCH, MICHAEL REESE HOSPITAL; ASSISTANT PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

(From the Cardiovascular Laboratory, Department of Physiology, Michael Reese Hospital, and the Department of Physiology, University of Chicago.)

Certain investigators have claimed that the electrocardiographic changes following recent coronary occlusions can determine the location of the resulting myocardial infarctions. Thus, Barnes and Whitten[1] reported that typical alterations of the *Q–R–S–T* complex occur in infarction of the left ventricle; an infarct in the anterior wall of the left ventricle producing a curve which belongs to the T_1 type of Parkinson and Bedford's classification[2]; and one in the posterior wall, a T_3 type of curve. However, Gilchrist and Ritchie[3] in their review of the literature of proven cases of recent coronary occlusion concluded that the available evidence did not lend support to the idea that the form of the electrocardiogram can be regarded as a definite localizing sign of infarction. This deduction is supported by the work of Saphir, Priest, Hamburger and Katz[4] and by analysis of the autopsied cases reported recently by Wilson and his coworkers[5] and by Wood, Bellet, McMillan and Wolferth.[6] While Wilson *et al.*[5] in their recent article stated that the location of the infarct plays an important rôle in determining the form of the ventricular complex, they nevertheless admit that many puzzling cases are met with when one attempts to correlate the electrocardiogram with the location of the infarct.

Barnes and Mann[7] claimed that in the dog following coronary ligation, a T_1 type of change occurred when the infarct involved the left ventricle and a T_3 type of change when it involved the right

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ventricle. Other investigations are not in accord with this interpretation. Thus, Feil, Katz, Moore and Scott,[8] Wolferth and Wood[9] and Harris *et al.*,[10] found a noticeable variability in the type of change in the electrocardiogram following ligation of the anterior descending branch of the left coronary artery. The first two groups of investigators observed that in some instances ligation of this branch of the coronary artery produced no changes in the electrocardiogram taken with the standard three leads.

Other attempts have been made to correlate the location of myocardial lesions with the type of change seen in the electrocardiogram. Thus, Crawford *et al.*[11] reported that, with rare exceptions, lesions produced in the anterior left ventricle of the cat's heart by means of a cautery gave rise to a T_1 type of electrocardiogram and located in the posterior left ventricle gave rise to a T_3 type of curve. A similar result was reported in the dog by Meek and his collaborators[12] using radon lesions, only one exception being found (a lesion in the posterior left ventricle failed to cause any change.) Meek *et al.*[12] further reported that lesions in the anterior wall of the right ventricle caused either no change or a T_1 type of electrocardiogram, and that lesions in the posterior wall of this ventricle had variable results. Robb[13] recently concluded that the type of electrocardiographic changes following myocardial lesions was determined by the group of muscle bands in which the lesion was produced. She reported that the superficial bulbospiral, deep bulbospiral, superficial sinospiral and the deep sinospiral bands each produces its own characteristic changes. Fowler, Rathe and Smith[14] found no correlation between the type of electrocardiogram and the location of the infarcts produced by tying small branches of the coronary arteries. It will be seen from the diversity of opinions expressed in the literature that the issue is not yet settled regarding the effect of the location of myocardial lesions on the electrocardiogram.

The present investigation was undertaken in an attempt to see whether or not injury and death of small sharply localized regions of heart muscles would produce characteristic alterations depending on the location of the lesion. For this purpose the ventricles were arbitrarily subdivided into 10 regions (Fig. 1). In order to make the results as clear as possible and to avoid the fluctuations in contour which occur from day to day in long term experiments because of the loose fixation of the dog's heart in the chest (Soskin, Katz and Frisch[15]), the destruction of muscle was produced as rapidly as possible and the changes followed for the first few hours.

Method. Dogs under morphin and sodium barbital anesthesia were used. The anterior chest wall was removed and artificial respiration instituted. The heart was placed in a snug cradle by suturing the split pericardium to the sides of the thorax, thus avoiding disturbing changes in position of the heart. The anterior chest wall was then replaced in order to restore approximately the usual chest contacts with the heart. A control electrocardiogram was recorded with the standard three leads, electrodes

TABLE 1.—SUMMARY OF DATA.

Exp. No.	Location of lesion.	Size of lesion.			T type of change.						Change in Q-R-S complex. Shift in electrical axis.†	Remarks.
					Early.			Late.				
		Endocardium mm.	Myocardium mm.	Epicardium mm.	Type	Degree	Time maximum change min.	Type	Degree	Time maximum change min.		
1	L. vent. ant. apex	8^2	22^2	15x6	T_2*	+++	1	T_2	++	240	Smaller L1, inverted L2 and 3. (Left)	Ventricular extrasystoles and paroxysmal tachycardia.
2	"	10^2	14^2	8x1	T_n*	+++	2	T_n	+++	240	Smaller all leads	
3	"	3^2	25^2	18x8	T_2	++	2	T_n	++	240		
4	"	2^2	10^2	15x3	T_1	+	$\frac{1}{2}$	0	....	..	Inverted L1, diphasic L2 and L3	
5	L. vent.	0	6^2	6^2	T_1	+	$\frac{1}{2}$	0	....	..		
6	ant.	0	10^2	5^2	T_1	+	1	T_1	+	120		
7	mid.	0	8x15	0	T_1	+	120	0	....	..	Inverted L1 (right)	
8	"	0	15^2	7x5	T_p	+	2	T_1	+++	120	Diphasic L2 and 3	
9	"	*:	15^2	10x2	0	....	..	T_1	+	240		
10	"	0	20x8	3x2	0	....	..	0	....	..		
11	"	0	10x6	0	T_2	++	$1\frac{1}{2}$	0	....	..	Q_1 and $_2$ developed	
12	L. vent.	0	8^2	0	0	....	..	0	....	..	Smaller all leads	
13	post. apex	0	20^2	10x4	T_2	++	2	T_2	+++	240	Smaller L3 Q_2 developed (left)	
14	"	*	20x7	0	T_2	+++	2	T_2	++	240	Q_2 and $_2$ developed	
15	"	20x8	15x8	*	T_n	+	2	T_n	+	240	Early inverted L1, later inverted L3 (right and left)	Paroxysmal ventricular tachycardia.
16	L. vent.	0	14^2	10x8	T_2	+	2	T_2	+++	240	Q_2 and $_2$ developed	
17	post.	2^2	30^2	11x6	T_2*	+++	2	T_2	+++	240	Smaller all leads	
18	mid.	2^2	40^2	12x10	T_2*	+++	2	T_n	+++	120	Inverted L1. Q_1 developed (right)	Ventricular extrasystole.
19	L. vent.	3^2	38^2	10^2	T_2	++	2	T_2	+	120	Q_2 and $_2$ developed	
20	post.	0	14^2	14x8	T_2	++	2	T_2	+	120	Smaller L3 (left)	
21	base	0	15x7	0	T_2	+	10	T_n	+	120		
22	"	0	15^2	10^2	T_2	++	2	T_2	+	240	Smaller L3 (left)	
23	R. vent.	3^2	9^2	8x3	0	....	..	0	....	..		
24	ant.	10^2	11^2	11x6	T_p	++	2	T_1	+++	240		
25	mid.	0	12^2	4x7	0	....	..	0	....	..	Larger L1, smaller L3 (left)	
26	"	10^2	19^2	15x5	0	....	..	0	....	..		
27	R. vent.	18^2	31^2	20x4	0	....	..	T_1	+	240		
28	ant.	1^2	15^2	10x1	T_1	+	10	T_1	+++	240	Q_1 developed	
29	base	5^2	25^2	8x5	T_2	+	2	T_2	+	240		
30	"	20^2	30^2	24x5	T_p	+	2	T_p	+	120	Q_2 disappeared	
31	"	2^2	15^2	10x5	T_1	+	2	T_1	++	120		Occasional ventricular extrasystoles.
32	"	0	25x5	15x4	T_p*	++	2	T_p	++	240	Larger L1. Q_1 developed (left)	
33	R. vent. post.	2x3	25^2	25x5	T_2	+	2	T_2	++	240	Larger L1 and 2 (left) Q_2 and $_2$ developed	
34	mid.	0	25^2	25x8	T_1	++	2	T_1	+	120	Smaller L3 (left)	
35	"	0	20^2	15x4	T_2	+	2	T_n	+++	240	Temporarily smaller L1 (right)	
36	"	12x5	22^2	20x6	T_2	+	2	T_2	+	240	Smaller L1, larger L2 and 3 (right)	
37	"	15x13	18^2	18x8	T_2	++	2	T_2	+	240	Smaller L1 and 2 negative L3	
38	"	25x7	26^2	22x6	0	....	..	0	....	..		
39	"	0	15x5	10x2	0	....	..	T_2	+	240	Larger L1 (left), Q_2 and $_2$ developed	
40	R. vent. post.	2^2	22^2	20x7	0	....	..	T_p	+	240	Smaller L2 and 3 (left)	
41	base	2^2	18^2	12x4	T_2	+	2	T_2	++	240	Smaller and later inverted L3 (left)	
42		10x17	15^2	12x2	0	....	..	T_2	+	120		
43		0	20^2	13x2	T_2	+	2	T_2	+++	120	Taller L2 and 3 (right)	
		R. endocardium	Myocardium	L. endocardium								
44	Vent.	0	20x30	0	T_1	+	120	T_1	++	240	S_2 and $_2$ appeared	
45	sept. ant.	0	20^2	*	T_1	+	2	T_1	+	240	Smaller L3, S_2 and $_2$ developed (left)	Occasional ventricular extrasystoles.
46	mid.	0	25x8	15x8	0	....	..	0	....	..	S_2 and $_2$ developed	
47	‡	0	10^2	0	T_p	+	120	T_p	+	240	S_2 developed	Occasional ventricular extrasystoles.
		Endocardium	Myocardium	Epicardium								
		0	25^2	20^2								

* Curve has monophasic appearance.
† The shift in axis is given in parenthesis.
‡ Location of lesion is in this instance in the interventricular septum anterior middle and left ventricule anterior middle.
NOTE: As shown in Fig. 1 the apex of the dog's heart is occupied entirely by the left ventricle and the basal portion anteriorly entirely by the right ventricle.
: A few spots show.

of German silver having been inserted beneath the skin of the two fore limbs and the left hind limb. The anterior chest wall was then temporarily removed and 1 cc. of 95% alcohol solution was injected into a predetermined area of the ventricular myocardium. (When injecting the interventricular septum the quantity of solution used was increased to 5 to 10 cc.) Care was taken to avoid involving the superficial coronary vessels. Following the alcohol injection the anterior chest wall was again replaced and a second electrocardiogram was taken as soon as possible ($\frac{1}{2}$ to 1 min.). Subsequent records were taken at approximately 2 min., 10 min., 1, 2 and 4 hr. after the injection. Following the last record the heart was removed. The position and area of the lesion produced by injection was then measured and its relation to the endocardium and epicardium was determined in the fresh specimen. These observations were later checked with Dr. M. Corrigan of the Department of Pathology, in the formaldehyde preserved specimen. The injected area was easily identified grossly both in the fresh and preserved specimens as a well-defined circumscribed region showing some hemorrhage. These lesions do not resemble infarcts histologically because the alcohol appears to act as a fixative, preserving the cytologic appearance for the few hours before the whole heart is fixed.

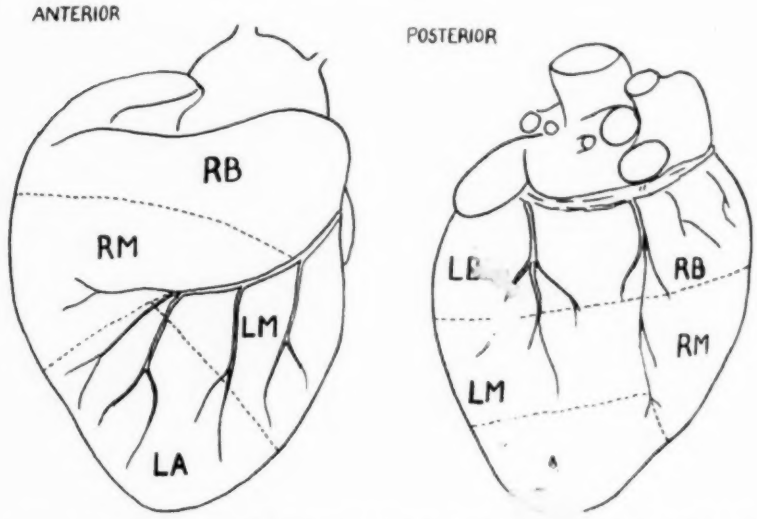

FIG. 1.—Diagram showing the subdivisions of the ante- d posterior surfaces of the heart used in this analysis. *LA.*, *LM.*, *LB.*, r respectively apex, middle and base of the left ventricle. *RM.*, *RB.*, repres vely middle and base of the right ventricle.

Results. The data of the 47 experiments are summarized in Table 1 and illustrative records of typical results are shown in Figs. 3 to 8. The subdivisions of the heart surface used are shown diagrammatically in Fig. 1. In addition the anterior interventricular septum was also injected. Fig. 2 shows the result in a control experiment in which 1 cc. of alcohol was injected into the left ventricular cavity. The electrocardiograms in this experiment showed no significant changes during the 4-hour period.

From Table 1 it will be seen that deep negative Q waves frequently developed in one or more leads following the production of the myocardial lesion (Figs. 6 and 7). In other experiments deep, negative S waves developed (Fig. 5). In many instances the electrical axis of the heart showed a noticeable shift following the production of the myocardial lesion (Fig. 4). Occasionally the amplitude of the Q–R–S complex decreased in all leads (Fig. 3).

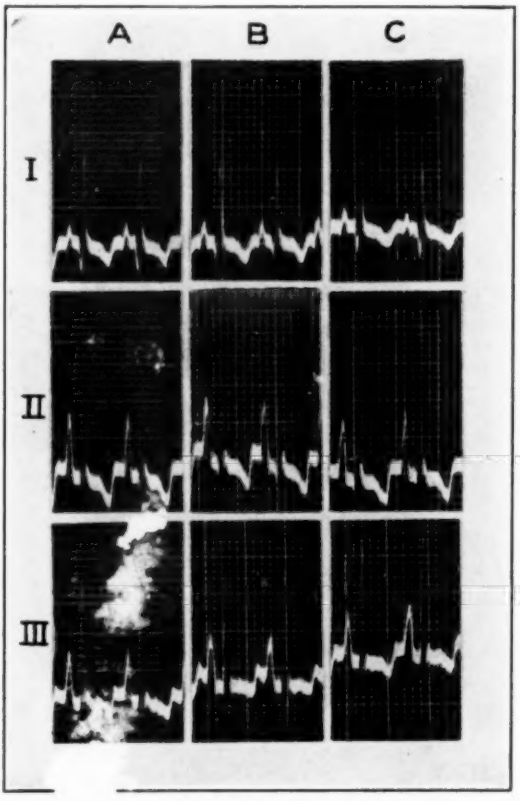

FIG. 2.—Electro[illegible]ams, standard three leads, in the control experiment in which 1 cc. of 95[illegible]was injected into the left ventricular cavity. Segment A was taken before the [illegible]ol injection; Segment B, 2 min., and Segment C, 4 hr. after the alcohol injection.

The appearance of a typical Q type could not be predicted from the location of the [illegible]yocardial lesion. When the Q type was classified according to the scheme of Wilson *et al.*, no constant correlation could be made between the location of the myocardial lesion and the Q type when it developed. (Compare experiment 16 with experiment 18). In this series, however, the anterior septal lesions were followed, without exception, by a Q_1 type of curve. The occurrence

of a shift in the electrical axis could not be predicted; nor, when it occurred, could it be accurately correlated with the location of the myocardial lesions. (Compare experiments 33, 34 and 39 with experiments 35 and 36, and experiments 40 and 41 with experiment 43.)

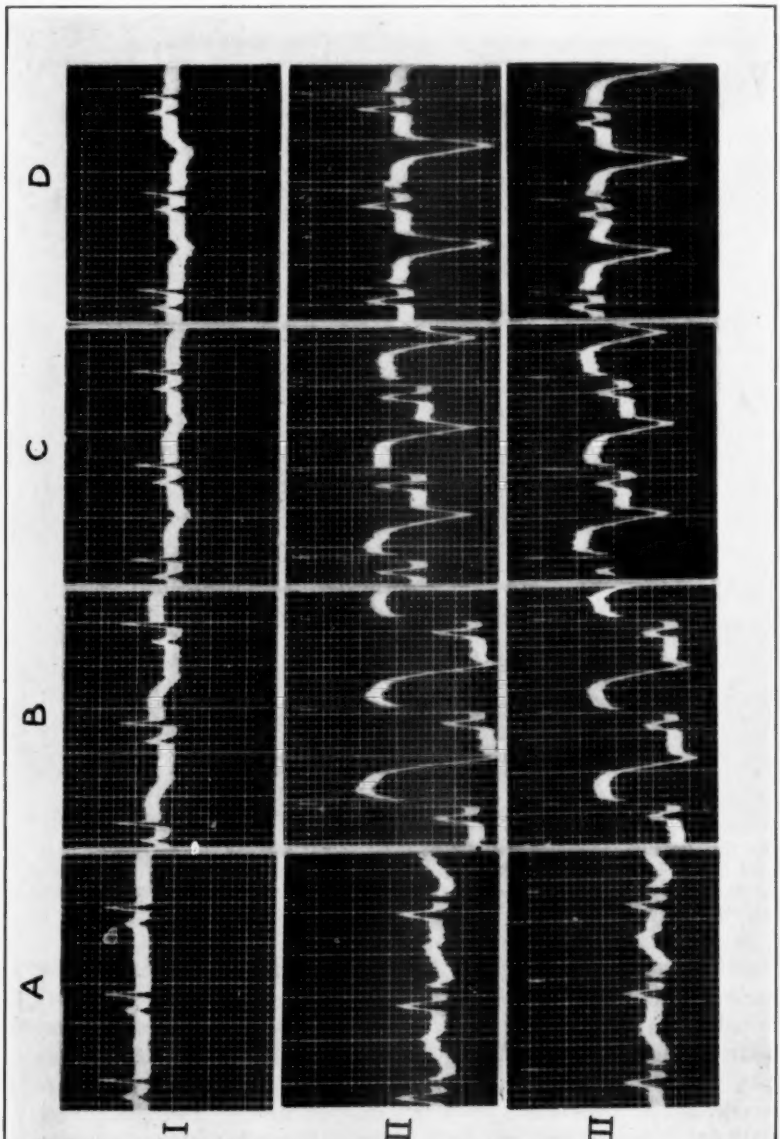

FIG. 3.—Experiment 2. Segment A control before production of myocardial lesion in the apex of the left ventricle anteriorly; Segment B taken 2 min., Segment C, 10 min. and Segment D, 4 hr. after lesion was produced.

Premature systoles and paroxysmal tachycardia followed the production of myocardial lesions in a few instances. These were all, with one exception, ventricular in origin.

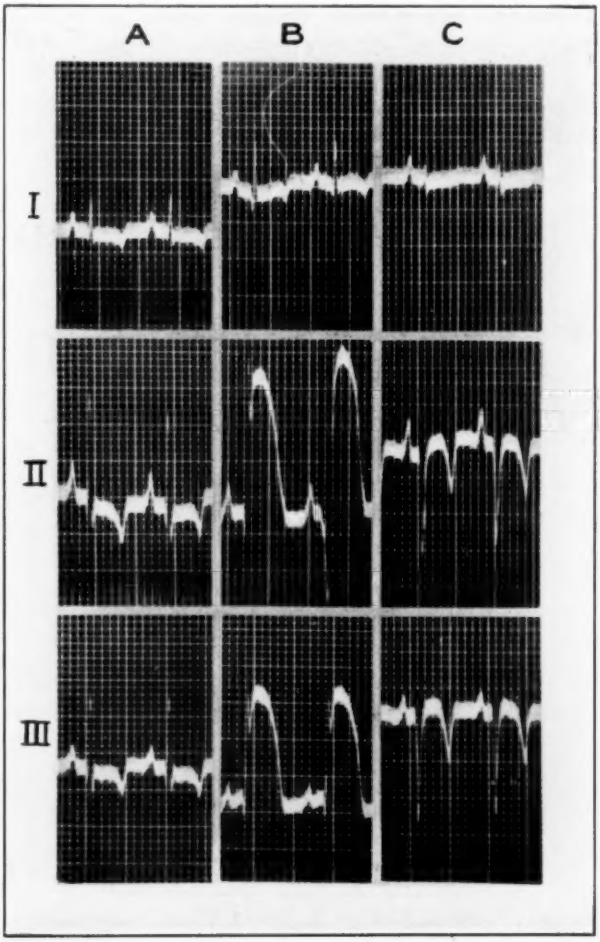

FIG. 4.—Experiment 1. Segment A control before production of myocardial lesion in the apex of the left ventricle anteriorly; Segment B taken 1 min. and Segment C taken 4 hr. after lesion was produced.

FIG. 3.—Experiment 2. Segment A control before production of myocardial lesion in the apex of the left ventricle anteriorly; Segment B taken 2 min., Segment C, 10 min. and Segment D, 4 hr. after lesion was produced.

It was found that the most striking change occurred in the S–T and T portions of the curve. Practically monophasic curves were seen a number of times soon after production of the lesion (Figs. 3 and 4). Very deep negative and very tall positive coronary T waves (Bohning and Katz[16]) were also found (Figs. 5, 6 and 7), the amplitude of which were on occasion as great as ± 25 mm.

When the changes in the $S-T$ segment and T wave were analyzed, the type of change found did not always fit into the T_1 or T_3 types of Parkinson and Bedford's classification. The changes observed in many instances fell into two additional subdivisions; one group in which the $S-T$ segment was at first positive in all three leads, and was later dominated by deep negative coronary T waves in all leads; and the other in which the $S-T$ segment was at first negative

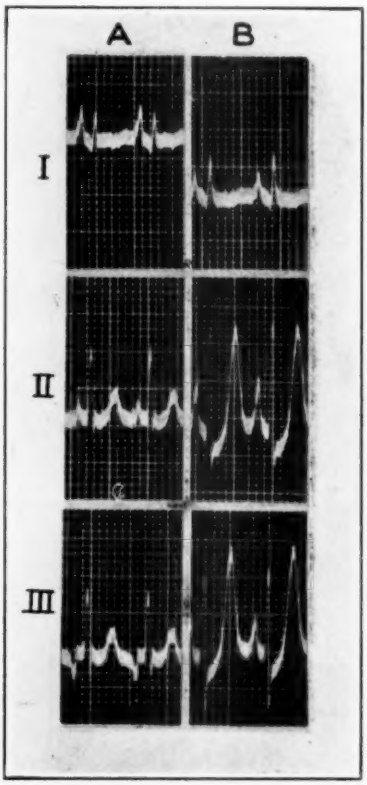

FIG. 5.—Experiment 8. Segment A control before production of myocardial lesion in the middle of the left ventricle anteriorly; Segment B taken 2 hr. after lesion was produced.

in all three leads and was later dominated by tall, upright, coronary T waves in all leads. The first of these types we have called the T_n type (Fig. 3) and the latter the T_p type (Fig. 8). In addition to these four types, a number of experiments showed no change at all. In some instances only the early stage, viz., the stage with marked $S-T$ deviation or only the latter stage, viz., the stage with marked T wave alteration occurred. In some experiments the early T type

based on the *S–T* shift was different from the *T* type which appeared later when the *T* wave alterations were at a maximum. Usually it was a T_p type changing to a T_1 type, or a T_n to a T_3 type or *vice versa*. However, we found no instance of a T_1 type changing to a T_3 type or *vice versa*. As a rule the changes in Lead I were not as marked as in Leads II or III. This is understandable since Lead I usually had the smallest complexes to begin with. Furthermore it happened frequently in the T_1 and T_3 types that the *S–T* and *T* changes were absent in Lead I or in Lead III, or that they occurred only in one of these two leads.

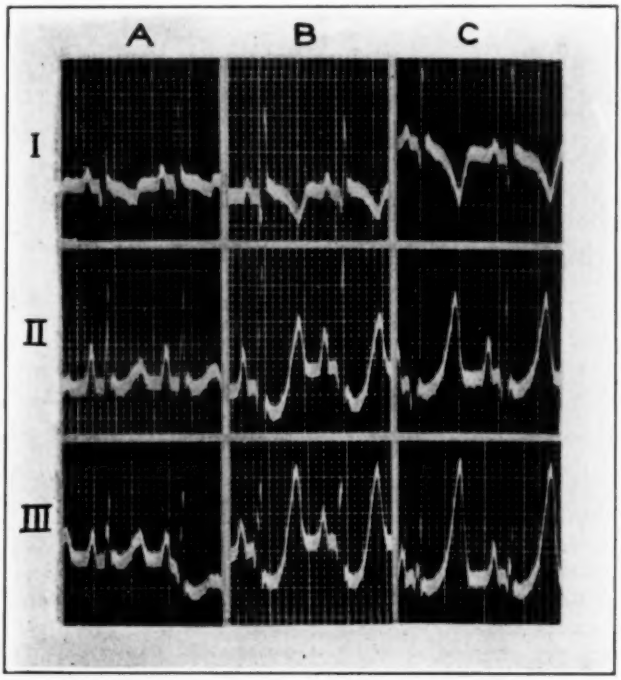

FIG. 6.—Experiment 28. Segment A control before production of myocardial lesion in the base of the right ventricle anteriorly; Segment B was taken 10 min. and Segment C, 2 hr. after lesion was produced.

Inspection of Table 1 shows that it is practically impossible to locate the site of lesion from the T type of the electrocardiographic changes. Even though the region were subdivided into relatively small areas the magnitude of change produced by lesions in the same locality was non-predictable. Sometimes a lesion in a given area was accompanied by no electrocardiographic change at all while in other instances a lesion in the same area caused a tremendous shift in the *S–T* segment resulting in a practically monophasic appear-

ance of the ventricular complex, followed later by tremendously inverted or strikingly tall coronary *T* waves. Furthermore, a lesion in one experiment gave a mirror image type of change to that caused by a lesion in the same locality in other experiments (compare

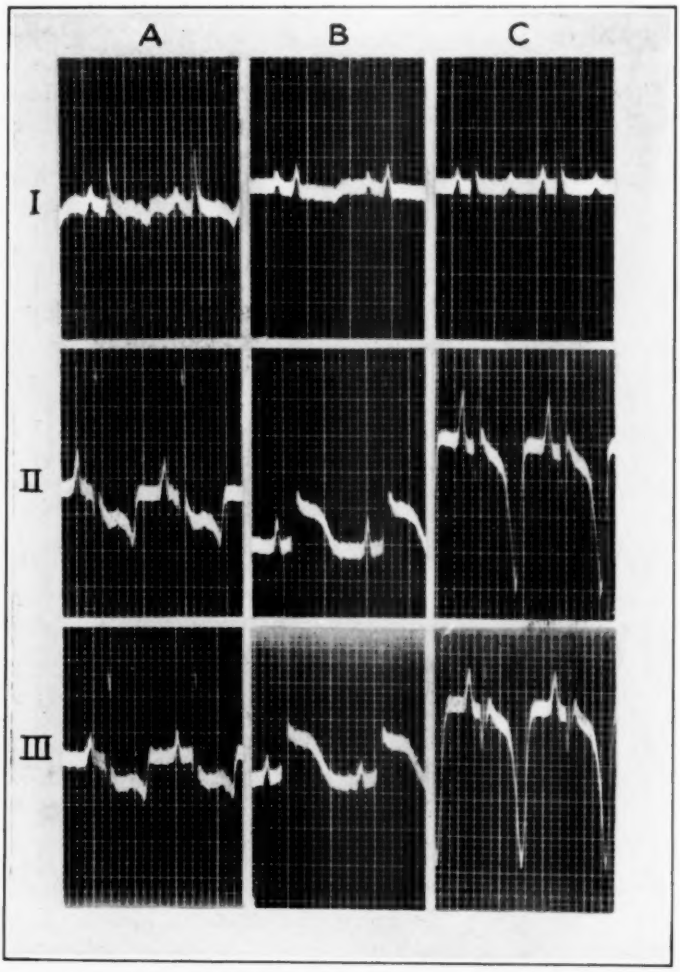

FIG. 7.—Experiment 13. Segment A control before production of myocardial lesion in the apex of the left ventricle posteriorly; Segment B was taken 2 min. and Segment C, 2 hr. after lesion was produced.

experiment 11 with experiments 5 to 10). This variability was apparently not dependent upon the size of the injured area nor upon the position of this area in relation to the epicardium and endocardium.

When an attempt is made to group the 10 small areas used for

injection into larger groups no constant differentiation can be made, as might have been anticipated from the literature, between effects of lesions in the right ventricle and those in the left, or between the effects of lesions located in the anterior wall and those in the posterior, or between effects of lesions in the basal portion of the ventricles and those in the apical portion. Lesions in the septum did not produce any characteristic change which differed from those produced by lesions in the outer walls of the ventricles.

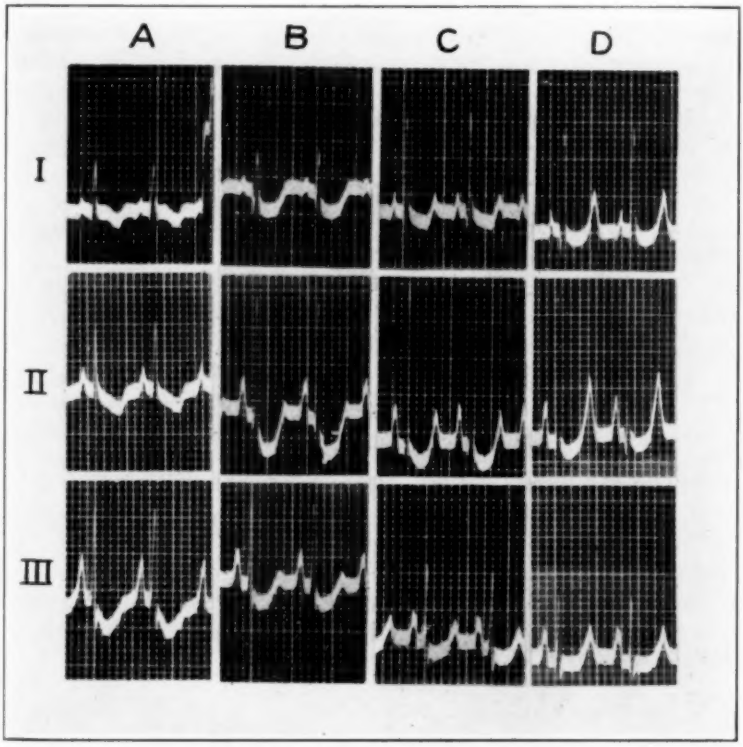

FIG. 8.—Experiment 32. Segment A control before production of myocardial lesion in the base of the right ventricle anteriorly; Segment B was taken 2 min., Segment C, 2 hr., and Segment D, 4 hr. after lesion was produced.

We are compelled to conclude on the basis of this study, either that the location of myocardial injuries is not important in determining the Q–T type of electrocardiographic change or at least that factors, as yet unknown, practically mask the influence of the location of the lesions in the heart on the electrocardiogram. While these lesions are not morphologically the same as infarcts and have a different genesis, they nevertheless produce the same type of "injury reaction" in the electrocardiogram. We therefore feel

warranted in applying these results to the "injury reaction" in the electrocardiogram following infarction as far as location of the lesion is concerned. We feel, therefore, that the view that the location of infarctions determines the Q–T type of electrocardiographic change does not rest on adequate evidence.

Summary. An analysis was made of the changes produced in the electrocardiogram during the first 4 hr. following injection of 95% alcohol into the dog's ventricular myocardium with the production of sharply demarcated areas of injury. Within a few minutes following injection of alcohol into the myocardium, monophasic ventricular complexes occurred several times. Deep inverted or tall upright peaked T waves having rounded shoulders and symmetrical limbs—negative and positive coronary T waves—were frequently found later. In addition to the T_1 and T_3 types of curves, two other types of change which we have called the T_p and T_n types occurred frequently. In the T_p type, positive coronary T waves occurred in all three leads preceded by negative S–T deviations. In the T_n type negative coronary T waves appear in all three leads preceded by positive S–T deviations.

On subdividing the ventricular myocardium into 10 regions, it was found that the location of the myocardial lesion did not determine the magnitude of the electrocardiographic change nor did it give rise to a characteristic Q–T type of change for any locality. It is concluded that using the standard three leads, the electrocardiogram cannot be used to differentiate (1) between injury to the anterior and the posterior wall of the ventricles; (2) between injury to the right and the left ventricle, and (3) between injury to the apical and the basal portion of the ventricles. No constant correlation could be made between the size of the injured area and the magnitude of electrocardiographic change in the standard three leads. The electrocardiographic changes apparently do not depend upon the location of the injured area in relation to the endocardium or epicardium.

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ARTERIOVENOUS FISTULA OF THE RENAL VESSELS.*

By Edward W. Hollingsworth, M.D.,
cardiologist, veterans administration facility,
hines, ill.

Arteriovenous fistula is a not uncommon condition, usually due to trauma, less often congenital, the limbs being the most usual sites. Pemberton[1] states that of 25 cases operated at the Mayo Clinic 16 were acquired. Of several seen at the Veterans Administration Hospital, Hines, Ill., all but 3 were the result of gunshot wounds. The present case is considered of interest because of its unusual location and probable etiology.

Osler,[2] in speaking of arteriovenous fistula, says: "On palpation the characteristic thrill is felt, vibratory, rough, continuous and increasing with the diastole† of the artery. Except in its roughness it is quite unlike any other thrill felt in cardiovascular lesions and is *pathognomonic*."‡ He later speaks of "the characteristic loud, rough, humming-top murmur, continuous, with marked intensification during the cardiac systole," and also refers to it as "machinery." He gives the important signs as the thrill and murmur, and the dilatation of the veins. Holman[3] includes slowing of the pulse, first noted by Branham,[4] and increase of diastolic blood pressure, upon closing the fistula, as further diagnostic points.

Osler[2] considered remote effects on the circulatory system rare, although 1 of his patients died of heart failure 31 years after the causative accident. Holman,[5] discussing its physiologic effects, says that 6 of 21 cases at the Johns Hopkins Hospital showed cardiac enlargement which he believes to be directly due to the fistula. Whether due to increased work, as claimed by Holman,[5] or deficient coronary circulation, as Lewis and Drury[6] believe, all observers now agree that cardiac enlargement and eventual failure are common.

Case Report.—M. S., a white male, aged 29, was admitted to the Edward Hines, Jr. Hospital, Hines, Ill., December 3, 1926, for treatment of chronic, active pulmonary tuberculosis. Family history was irrelevant,

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† Apparently a typographical error, systole being intended.

‡ Italics are author's.

no near relative had tuberculosis. The patient served in the U. S. Army from May to December, 1918. At the time of discharge he felt tired and weak and did not work for 2 or 3 months but then worked steadily until October, 1926. He had renal colic in July, 1925, and was in hospital 1 month, being told that he had a kidney stone. In October tuberculosis of the kidney was diagnosed and removal advised. This was done November, 1926, through the usual lumbar incision, the ureter being removed through the left rectus and the patient was discharged 6 weeks later. For 2 weeks prior to the operation he had a severe cough which gradually subsided.

At the time of admission the wound over the kidney region showed a slight serous discharge and had not entirely healed until the latter part of July. The blood pressure was 110/70 and no abnormal cardiovascular

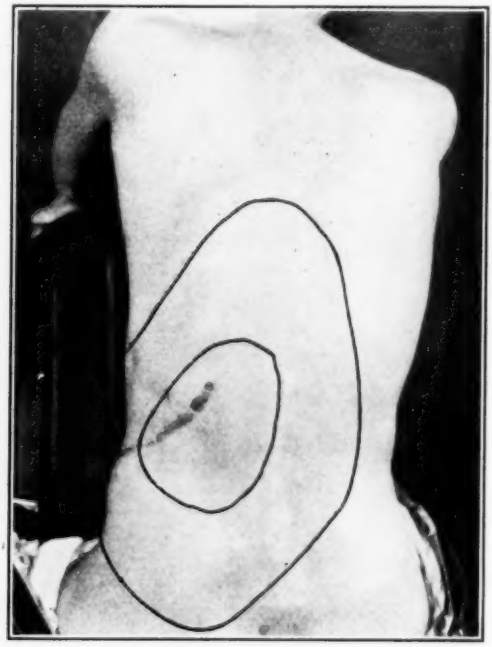

FIG. 1.—Photograph taken June, 1930, showing areas of transmission of thrill (small circle) and bruit (large circle).

findings were noted; chest examination and roentgenogram showed a far advanced pulmonary tuberculosis. January 31, 1928, the patient had pain in the left kidney region, and for a time a septic temperature and rapid pulse, which later became normal, and he was discharged at his own request June 22, 1930, as unimproved.

He was readmitted January 19, 1931, and a psoas abscess found. A body cast was applied and after several months replaced by a corset, with marked relief of symptoms. Genito-urinary examination revealed tuberculosis of the right kidney and bladder. He again had a septic temperature, which gradually fell to normal. The blood Wassermann and Kahn tests were negative, urinalysis and blood counts normal.

The patient was seen by the writer February 27, 1930, his ward surgeon having made a diagnosis of aneurysm. He stated he had first "felt a noise"

over the kidney scar in May or June of 1928 but had no other symptoms referable to the cardiovascular system. Radial pulses were somewhat water-hammer in type, there were no murmurs and no sclerosis of the peripheral arteries. The heart was enlarged to the left, the border being percussed 10 cm. from the midline, impulse forcible. The rate was 90, blood pressure 114/60. A thrill and bruit were present over the nephrectomy scar, the former over a small, the latter over a relatively large, area (Fig. 1). Both were accentuated in systole and were not transmitted down the aorta or its branches and it was found that they could be stopped by bimanual pressure over the back and abdomen* without affecting the pulsations of the aorta, the heart rate falling to 72 and the blood pressure rising to 124/80. The patient experienced no sensation such as Reid[7] describes. There were no superficial dilated or tortuous veins in the neighborhood.

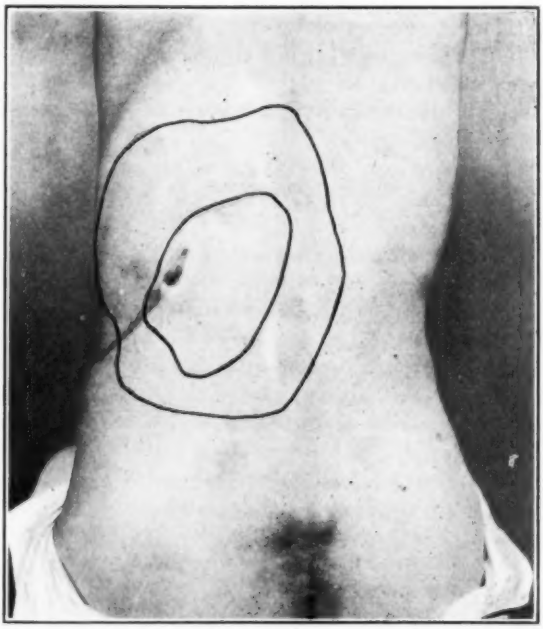

FIG. 2.—Photograph taken July, 1932, showing diminution in areas of transmission of thrill and bruit.

Electrocardiograms were normal on several occasions. Roentgenograms showed an increase of 2½ cm. in the transverse diameter of the heart in less than 3 years although there was roentgenologic and clinical evidence of improvement in the pulmonary tuberculosis. Blood volume[8,9] was found to be 4916 cc. on December 6, 1931, and 5196 cc. on February 25, 1932, normal for patients' weight of 117. At this time the patient is quite comfortable and his general condition, as well as the psoas abscess and lung tuberculosis, are showing improvement.

Discussion. The question of diagnosis is interesting. The thrill and bruit are indicative of an aneurysm, their intensity and large

* Tracings were taken under similar conditions in 3 other cases—in 2 there was no change in rate, in the third a slight increase.

area of transmission suggest the involvement of large vessels. An arteriovenous one was suggested by the continuous thrill and bruit, "machinery" in type, with systolic intensification, the secondary effects on the general circulation, the characteristic reaction to what was believed to be closure of the fistula, and progressive cardiac enlargement. Because of the location of the thrill and bruit, and known trauma to the renal vessels, it was believed that they were the ones involved; the absence of dilated and tortuous superficial veins indicated the lesion was deep, the absence of aortic thrill and bruit suggested that a branch only was affected and there were no localizing findings pointing to any other intraäbdominal vessels.

Arterial aneurysms of the renal artery are generally regarded as rare. Thus, Conroy,[10] in a recent review lists only 32 cases and states that this is one of the rarest, if not the rarest, of all sites. Mathé[11] says that they constitute about 1% of all aneurysms and the diagnosis is extremely difficult. Singer[12] reports 2 cases and thinks the condition is much commoner than is generally believed to be the case. So far as could be ascertained but 1 case of arteriovenous aneurysm of the renal vessels has ever been reported.[13] The patient was a white male aged 27, who when first seen had congestive heart failure, which grew progressively worse until death. There had been no operation, there was no history or evidence of trauma and the diagnosis was made with considerable hesitation but verified at autopsy. Holman[14] states that he knows of no similar case.

The normal blood volume was at variance with the belief of Holman[3,5] but in accord with results obtained in other cases at this hospital[15] and in the case of Ellis and Weiss.[16] Oxygen content of distal vessels of course could not be determined. No systolic apical murmur was noted. Ophthalmoscopic examination did not disclose any pulsation of the retinal vessels and no definite changes in the size or shape of the heart, described by other authors,[3,6,16] were found upon closure of the fistula, possibly due to incomplete closure, particularly difficult with the patient in the erect position.

Postoperative infection, trauma at operation and tuberculosis must be considered possible etiological factors. A–V communications following the trauma of operation[17] are not rare, there being many cases reported. Tuberculous involvement of large blood-vessels is generally accepted as rare. Baumgarten and Cantor[18] were able to collect but 20 cases of tuberculous aneurysm of medium-sized and large arteries. They mention no case of arteriovenous aneurysm.

Dr. McDougall, staff urologist, investigated the technique employed and states that the renal artery and vein were ligated separately at operation, a procedure calculated to obviate any possibility of such a complication as apparently occurred. The ligatures, however, were passed by means of an aneurysm needle which might account for some additional injury to the vessels. The patient

refuses operation, although this has not been strongly advised, and believes the thrill and bruit are becoming less. By comparing photographs (Figs. 1 and 2) of the areas of transmission, taken some 2 years apart, it would seem that this is so. Spontaneous healing has been noted in small arteriovenous communications experimentally produced,[19] and of course may be taking place in this case. There has apparently been no increase in the cardiac involvement for some time, so the prognosis may be better than originally feared.

Summary. A case is reported in which signs and symptoms suggesting an arteriovenous aneurysm appeared over the site of a nephrectomy scar some 18 months following operation. Progressive enlargement of the heart was noted for a time but the size has now apparently become stationary.

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LARGE DOSES OF TUBERCULIN IN TESTING GUINEA PIGS INOCULATED FOR DIAGNOSTIC PURPOSES.*

By Thomas B. Magath, M.D.,

ASSOCIATE IN SECTION ON CLINICAL PATHOLOGY, THE MAYO CLINIC; ASSOCIATE PROFESSOR OF CLINICAL BACTERIOLOGY AND PARASITOLOGY, THE MAYO FOUNDATION, ROCHESTER, MINNESOTA.

The value of inoculating guinea pigs with clinical material in which Mycobacterium tuberculosis cannot be found by direct examination of smears has repeatedly been demonstrated. By this

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biologic test many diagnoses have been made and confirmed when all other laboratory tests have failed.

Since clinical application of the test became general, attempts have been made to shorten the time necessary for diagnosis. If the animals die before 3 weeks after inoculation and tuberculous lesions cannot be found, the test should be considered a failure. Animals should not be killed until at least 8 weeks after inoculation. If spontaneous death occurs between the 3d and 8th weeks, and if lesions of tuberculosis cannot be found, the test should then be reported as negative.

A method advocated by Bloch is to inject the material into the region of the inguinal glands of the animal and then, with the thumb and finger, to traumatize the inguinal lymph nodes gently. This is supposed to cause early involvement of these nodes and thus hasten the diagnosis. Sufficient protocols illustrating the usefulness of this method are lacking, and its advantage is open to question when used with material having other organisms present in it.

Another means of hastening the development of tuberculosis in guinea-pigs by exposing them to a small dose of irradiation with Roentgen rays was amplified by Morton after several investigators had proposed it. The hypothesis in this procedure is that irradiation will reduce the resistance of the animal to such a point that the organisms develop more rapidly. Practically, the dose is so difficult to control and the resistance of the animals varies so much that the method is not suitable for routine use. As a rule, either the animals are killed by an excessive dose or no effect on the outcome of the tuberculous process is obtained.

Occasionally, suggestions have been made that a strain of guinea pigs genetically susceptible to tuberculosis should be developed. Sewell Wright did develop such a strain by inbreeding, but the loss of animals is too great to sustain the strain, and it is not practicable to obtain and maintain such animals.

A technique designed to hasten the development of lesions by direct injection into certain organs, for example, into the liver or eye,[8] has been proposed. The procedure is useful in certain instances but animals are often killed by it, or die a few days after as a result of hemorrhage or infection. In the long run, the time is not greatly shortened and, on account of this, together with the initial loss, the uncertainty of actually injecting the material into the organ, and the necessary limitation of the amount that can be injected, the method is not recommended as a routine procedure.

An interesting modification of this method has been to inject the material into the mammary glands of an animal with the expectation of recovering the organism in the milk. Obviously this method is lacking in practicability.

Magath and Feldman attempted to hasten the diagnosis by injecting material into the brains of guinea pigs. Two hundred

and eleven specimens were inoculated intracerebrally and the results compared with the routine method. The routine method yielded 31 positive specimens, the intracerebral method only 11. Diagnosis was made in these 11 cases after an average elapsed time of 30 days, whereas the elapsed time in the routine tests was 49 days. Although the intracerebral method did hasten the diagnosis, the number of failures and negative results clearly demonstrated the shortcomings of the method and proved its unsuitableness as a routine procedure.

Murphy and Ellis found that splenectomized mice survived inoculation with bacilli of tuberculosis for a shorter time than controls did, but routine procedure based on this principle is out of the question.

Schulz recommended injecting material intracutaneously, and stated that this would hasten the results. With contaminated material, however, nonspecific abscesses occur, and Schulz himself did not furnish a protocol to substantiate his claims.

Aside from these and other more or less mechanical devices for hastening the development of tuberculosis in these diagnostic animals, investigators have used cutaneous or intracutaneous methods of testing with tuberculin. They have employed doses somewhat comparable to those used in the diagnosis of tuberculosis in man as, for example, 0.1 cc. of a 5% solution. In order to obtain results easiest to read, only white guinea pigs should be used, and the area of injection should be carefully shaved or plucked, or the hair removed by a chemical process, so as not to cause minute abrasions.

The intracutaneous method was devised by Römer, used by Esch and Schürmann, and extensively tested by Graetz. These investigators found that positive reactions often occur in animals 10 to 12 days after inoculation with material containing bacilli of tuberculosis. In applying this method, the rule is to begin testing the animals after 2 weeks, and then to test them every 2 weeks thereafter. Although all of these investigators indicated some errors in their series and others condemned the method on several grounds, consideration of their protocols confirms the conclusion that the test is useful and hastens the positive diagnosis in the majority of cases by from 3 to 5 weeks. Nevertheless, the method requires a careful technique and a considerable amount of time in order to prepare and test the animals. When positive reactions occur at the first test, necropsy must be carefully performed and sectioning frequently resorted to.

The loss of weight has been useful under certain circumstances as an indication that an animal was infected, but if animals are kept in their cages under proper conditions and given good care and food, loss of weight does not become a practical criterion for selecting animals for necropsy before the standard time allotted.

Some years ago Dr. Louis Gross, of Mount Sinai Hospital, New York City, called my attention to a method that he was using. He injected 0.5 cc. of tuberculin subcutaneously into his test animals from 3 to 4 weeks after the original inoculation with the suspected clinical material. In most animals with infection sufficiently advanced by that time, death resulted promptly, and the diagnosis was thus hastened by several weeks. This method was used by Esch and compared with Römer's method; however, the material tested was a pure culture of Mycobacterium tuberculosis. Esch concluded that the intracutaneous test was superior.

Experimental Observations. After preliminary tests indicating that normal animals were not killed by so large a dose of tuberculin, it was decided to use the method as a routine in our standard technique as follows: The clinical material was centrifugalized for 1 hour at 2500 r. p. m. in a centrifuge with a head-radius of 13.5 cm. At the end of this time 1 cc. at the top was pipetted off and, after the middle portion had been discarded, this top portion was added to the sediment. The whole was now made up to 5 cc. with physiologic saline solution, and 2 guinea pigs were given injections through the abdominal skin, 1 subcutaneously and 1 intraperitoneally. If a guinea pig died and no gross lesions were evident before 3 weeks had passed, the test was considered a failure; if a guinea pig died and no lesions were present after 3 or more weeks had elapsed, the test was considered negative. If both animals were alive at the end of 4 weeks, the one receiving the intraperitoneal injection was tested by injecting 0.5 cc. of OT tuberculin subcutaneously. If it died and was found to be positive, its mate was sacrificed and examined. All other guinea pigs were permitted to live for 8 weeks and, at the end of that time, were killed and considered either positive or negative depending on whether lesions were present or absent. To anyone experienced in the diagnosis of tuberculosis in such animals, gross lesions can be diagnosed accurately without resorting to histologic examination of tissue. In certain cases, especially when the animal died early, the histologic diagnosis of tuberculosis was used and was based primarily on finding acid-fast bacilli within the lesions. In this series, histologic confirmation of a tentatively positive or negative diagnosis was resorted to 7 times.

In order to compare the advantage of testing with tuberculin, a similar series of animals (400 pairs of guinea pigs or 200 specimens) were injected and studied; the same routine was used but testing with tuberculin was omitted.

Table 1 indicates that the animal injected intraperitoneally is much more likely to become infected than the one injected subcutaneously, but Table 2 reveals the interesting fact that the animal injected intraperitoneally is more likely to die before 3 weeks, thus

resulting in a failure. It occasionally happens that animals injected subcutaneously become positive when their mates are negative,

TABLE 1.—AGREEMENT AND DISAGREEMENT AMONG GUINEA PIGS INJECTED INTRAPERITONEALLY AND SUBCUTANEOUSLY (400 PAIRS, CONTROL; 400 PAIRS, TUBERCULIN TESTED).

Positive, intraperitoneal*	
Control	10
Tuberculin tested	11
Negative, intraperitoneal†	
Control	2
Tuberculin tested	3
Positive, intraperitoneal‡	
Control	29
Tuberculin tested	58

* Mates negative, subcutaneous.
† Mates positive, subcutaneous.
‡ Mates positive, subcutaneous.

TABLE 2.—DISAGREEMENTS AMONG 400 PAIRS OF CONTROL GUINEA PIGS, DURING THE PERIOD WHEN 400 PAIRS OF TUBERCULIN TESTED GUINEA PIGS WERE INJECTED.

Method of injection.	Result.	Number of specimens.
Subcutaneous	Failure	12
Intraperitoneal	Negative	
Subcutaneous	Negative	42
Intraperitoneal	Failure	
Subcutaneous	Failure	1
Intraperitoneal	Positive	
Subcutaneous	Positive	4
Intraperitoneal	Failure	
Subcutaneous	Failure	12
Intraperitoneal	Failure	

TABLE 3.—COMPARISON OF CONTROL AND TUBERCULIN TESTED GUINEA PIGS, (400 PAIRS, CONTROL; 400 PAIRS, TUBERCULIN TESTED).

	Control.		Tuberculin tested.	
	Number.	Per cent.	Number.	Per cent.
Positive specimens, urine	25	57	39	55
Positive specimens, other material	19	43	33	45
Positive specimens, total	44	11	72	18
Both guinea pig failures	7	1 7	5	1.1
Average elapsed time before diagnosis	53 days		33 days	

TABLE 4.—TUBERCULIN TESTED GUINEA PIGS (400 PAIRS).

Guinea pigs positive and killed by tuberculin	54 (78.3%)
Guinea pigs positive but not killed by tuberculin	15 (21.7%)
Guinea pigs negative but killed (?) by tuberculin*	5
Mate positive	1
Mate negative	4
Guinea pigs negative (not killed by tuberculin); mates positive	2

* These animals died within 48 hours after administering tuberculin, but this number of animals might have been expected to die even if not tested with tuberculin.

and from Table 3 these observations may be strengthened by noting the larger number of positives among the animals injected intraperitoneally when animals injected subcutaneously were failures.

In the series there were a total of 44 positive specimens in the control group and 72 in the tuberculin group (Table 3). In the control group, 7 (1.7 per cent) pairs of animals were failures, whereas during the period when the 400 pairs of tuberculin tested animals were being observed, 5 (1.1 per cent) pairs were failures.

With the exception of 1 or 2 animals that died following administration of tuberculin and had tuberculous lesions, all animals died within 48 hours. This resulted in a positive diagnosis in 54 (78.3%) within 30 days after inoculation. The average length of elapsed time in the whole series was 33 days for a positive diagnosis as compared to an average elapsed time of 53 days in the control series.

Fifteen (21.7%) of the positive animals so tested did not die as a result of the tuberculin, but nevertheless, were found to have tuberculosis when they eventually came to necropsy.

Five animals died within 48 hours after receiving tuberculin, but were negative. This does not necessarily mean that the injection killed them, for approximately this number of animals might have been expected to die from other causes. Of the mates of the 5, 1 was tuberculous. In the series, 2 mates were positive when the tuberculin tested animals were negative and survived the full 8 weeks.

Comment. It is easy to understand why intraperitoneal injections should be fatal more often than subcutaneous injections, since much of the injected material contains pyogenic organisms; but, when injections of equal amounts are made into both animals, just why the animals injected intraperitoneally should more often be positive is not altogether clear.

This balancing of subcutaneously and intraperitoneally injected animals against each other is important and suggests again the desirability of using this procedure as a routine. Similar results were noted previously by Magath and Feldman.

It is apparent that this method of testing with tuberculin will not result in every positive animal being killed promptly, but from the evidence presented more than three-fourths will succumb within 48 hours. Of those not dying as a result of the tuberculin, the chances that any given animal will present evidence of tuberculosis later on is only 1 in 30. A dose of 0.5 cc. of OT tuberculin does not kill a guinea pig that does not have tuberculosis. Hence, the procedure is safe for routine use.

The use of tuberculin by this method clearly results in shortening the time necessary for the animal diagnosis of tuberculosis by about 3 weeks. The length of time compares favorably with that required for diagnosis by cultural methods. That more specimens can be

demonstrated to contain bacilli of tuberculosis by injection of guinea pigs than by cultures has been demonstrated by Magath and Feldman and by others.

In a series reported with material in which organisms could not be demonstrated microscopically, the average length of elapsed time for cultures was 40 days, for guinea pigs 43 days; however, 14 specimens were proved to contain Mycobacterium tuberculosis by animal inoculation, whereas only 4 were so demonstrated by cultural methods. In material known to contain organisms by microscopic demonstration, the average elapsed time for diagnosis was 36 days by cultural methods and 46 days by inoculation of guinea pigs. Four specimens yielded no growth on culture, 2 specimens resulted in failures in both guinea pigs, and 1 gave negative results.

The value of the tuberculin test must be weighed against its cost. This will depend to a great extent on the number of animals tested routinely. If tuberculin can be purchased in large quantities, a reasonable price may be obtained. Against this cost must be placed the saving in care and food of these animals for 3 weeks and the advantage of destroying tuberculous animals early. Of course the value to the patient of an earlier diagnosis cannot be placed on a basis of dollars and cents but, actually, the total additional cost of using tuberculin is not great and is far outweighed by its benefits.

Conclusions. When testing clinical material for the presence of Mycobacterium tuberculosis by animal inoculation, a pair of guinea pigs should be inoculated, one subcutaneously and the other intraperitoneally. In order to hasten the test, one or both animals should be tested at the end of 4 weeks with 0.5 cc. OT tuberculin injected subcutaneously.

More than three-fourths of the positive animals will be killed within 48 hours and the diagnosis hastened by 3 weeks. The chances that any other given animal will later prove to have lesions of tuberculosis is 1 in 30.

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SO-CALLED "PRIMARY" TUBERCULOSIS OF MUSCLE.

By Henry Milch, M.D., F.A.C.S.,
ASSOCIATE ATTENDING ORTHOPEDIST, HOSPITAL FOR JOINT DISEASES; ADJUNCT SURGEON, RIVERSIDE HOSPITAL; INSTRUCTOR OF ANATOMY, COLUMBIA UNIVERSITY MEDICAL SCHOOL,
NEW YORK CITY.

(From the Orthopedic Service of Dr. Harry Finkelstein at the Hospital for Joint Diseases.)

Tuberculosis of muscle, the consequence of a contiguous tuberculous focus, with fistula formation, is not unusual. On the other hand, so-called primary muscular tuberculosis, in the sense of a metastatic, hematogenous infection, secondary to a tuberculous infection elsewhere in the body, is a great rarity. True primary tuberculosis of muscle (*i. e.*, first lesion in muscle) is not known to exist. No less an authority than Virchow doubted the existence of the so-called primary form. However, up to 1932 Hanke[1] noted the record in the literature of about 55 cases of well-authenticated tuberculosis of muscle other than by direct extension. To this must be added the cases described by Ceccarelli[2] and Prussia.[3] In the great majority of the cases the muscles of the extremities were involved. These included the quadriceps, gluteus, palmaris longus, biceps, triceps, flexor and extensor of the finger, abductor pollicis, etc. In the others, the sternomastoid, pectoralis, rectus abdominis and lumbar muscles have been affected (See also Meyerburg[7]). In 1 case, the only one on record, reported by Zahnert,[4] the tendon itself, of the triceps humeri, was the seat of the tuberculous infection.

We have seen several cases in which the pectoralis major became involved following operation for tuberculous axillary glands. But the following is the first which we have observed, where the tuberculosis appeared to be independent of any contiguous focus.

Case Report. M. S., female, aged 28, was admitted to the hospital in January, 1934, with swelling behind the left knee. The patient has been under observation for many years for a Pott's disease of the spine, with a collapse of the lower dorsal vertebræ. About 10 years ago she developed symptoms in the right knee and a plaster-of-Paris bandage was applied, with resulting stiffness of the knee. One year ago the patient noted pain and enlargement of the left knee, without any apparent cause. There was no malaise and only slight, if any, fever. Motion of the knee was hardly interfered with. About 3 months later a painless, soft swelling appeared behind the left knee joint and she presented herself at the Out-Patient Department. The skin over this mass was not hot or red. Material aspirated from the mass and injected into a guinea pig was reported as being negative for tuberculosis. Since that time the swelling continued to increase in size and the patient began to complain of pain in the anterior portion of the knee, which became definitely enlarged.

On her admission to the hospital on January 15, a large gibbus in the lumbodorsal area, due to a tuberculosis of the spine, was noted. The right knee was subluxated posteriorly and was ankylosed in slight flexion.

FIG. 1.—Photograph of swelling in back of leg.

FIG. 2.—Rœntgen photograph of outline of abscess after attempted injection with contrast medium. Note absence of bone involvement.

FIG. 3.—Wall of tuberculous abscess cavity in muscle. Note tubercle in upper left-hand corner and portion of caseating mass still present in abscess cavity. (×13.)

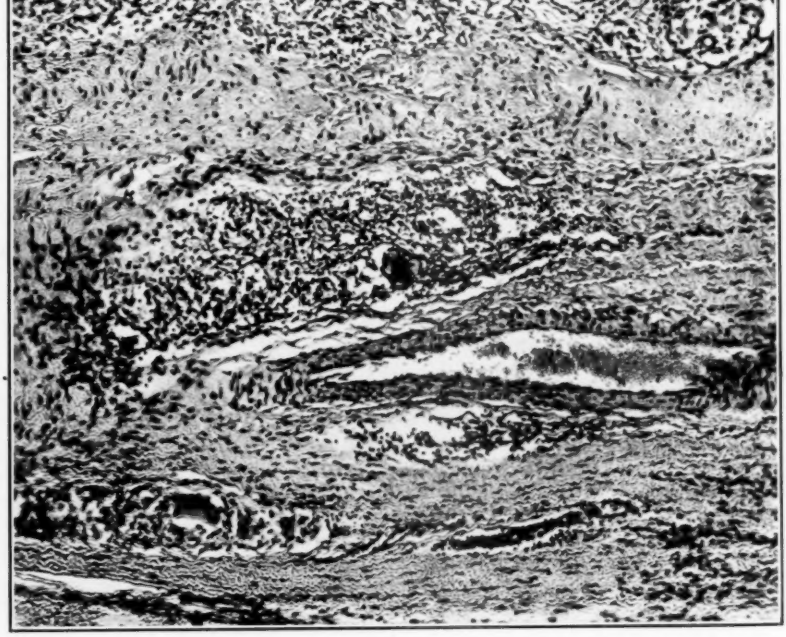

FIG. 4.—Portion of abscess, showing cell exudate with two Langhans giant cells and dense fibrous tissue. (× 150.)

The left knee was definitely enlarged, mainly on its posterior aspect. The tissues about the joint were thickened, but there appeared to be no fluid in the joint. Motion was possible from 180 degree of extension to 120 degrees. There was no abnormal anteroposterior or lateral mobility. On the inner aspect of the left leg, just below the flare of the medial tibial condyle, there was a tense, elliptical, semielastic swelling about 10 cm. in its greatest length (Fig. 1). The skin over this mass was apparently perfectly normal in color, texture and consistency. The mass was not adherent to the skin, but seemed to be fixed to the underlying muscle. On attempting to aspirate this mass, the needle seemed to penetrate into a large cavity, but no fluid could be withdrawn. When the needle was removed, the lumen was found plugged with a gelatinous material. Subsequent examination of this material revealed nothing upon which a diagnosis could be based. Culture was reported sterile. Roentgen ray of the knee was reported by Dr. Pomerantz as showing "the articular surfaces of the femur and tibia to be normal. The joint space is not narrowed and there is no erosion of the articular surfaces of the bones comprising this part. On the posterointernal aspect of the knee a circumscribed, soft tissue mass is visualized within which no calcific deposits can be seen. There is, in addition, distinct distention of the suprapatellar pouch." On the 18th the quantitative tuberculin test was reported as strongly positive. The following week an effort was made to inject the mass with a contrast medium, but this was only partially successful because of the great resistance within the swelling, and stereoscopic roentgenograms were reported as disclosing an "irregularly injected soft tissue mass in the popliteal region the character of which cannot be radiographically determined" (Fig. 2). From these findings a definite diagnosis could not be reached, though it was believed that the condition was either a mucoid tumor or an enlarged bursa.

Operation was performed on January 25 under general anesthesia. When the tissues were exposed, it was found that the mass was entirely localized to the inner head of the gastrocnemius muscle, which was with slight difficulty isolated from its origin on the femur down to its union with the outer half of the muscle. The mass was enveloped by a dense, fibrous capsule, from which a thin layer of muscle fibers arose. During the course of the dissection the sac was accidently ruptured and a large amount of dry, grayish, granular, caseous material extruded. The irregularly roughened sac occupied the center of the medial head of the gastrocnemius and extended from within about one-half inch of the origin of the muscle to just above its union with the outer head. For the first time, the suspicion of tuberculosis of the muscle arose. There was no connection whatsoever with the joint. In amputating the muscle at its femoral origin, the joint was opened for a distance of about 1 cm., but that portion which could be examined through this small opening appeared to be normal in color and without excess of fluid. The rent was repaired, the wound was swabbed with iodin and closed in layers. Convalescence was uneventful and primary union had occurred by the time the sutures were removed. Subsequently a small fistula developed, but this responded to conservative treatment.

At the present time the condition appears to be completely quiescent. There has been no loss of range of motion in the knee. There is no pain and no evidence of any fluid or other acute symptoms in the anterior compartment of the knee joint, though arthroscopy of the knee performed on February 19 by Dr. Berman, showed a "large mass of fat in villus and in pad formation throughout the knee joint. In many areas this showed the appearance of chronic inflammation. The under surface of the patella showed slight opacity of the cartilage, but no definite erosion could be made out. The internal meniscus was seen in one-half of its extent and seemed normal. It was not possible to see the internal, femoral condyle clearly,

because of the large mass of fat, which obscured it. Several biopsy specimens were taken."

The Pathological Diagnosis: "Tuberculosis of the synovial membrane." The mass of muscle tissue previously removed was reported by Dr. Jaffe in the following sense:

The gross specimen consists of numerous large pieces of tissue. One of them is very tough and fibrous, being apparently made up of tendon and being in a shape of a sac, the whole measuring 10 cm. in length. The lining is rough and apparently somewhat friable. Another piece is quite irregular in shape and cystic to palpation. It measures 4 cm. in diameter. Upon section it is seen to be a very much softened mass of partly pinkish and partly whitish tissue. Most of the other pieces are extremely friable masses of white tissue, with which a mass of fibrinous exudate is in some areas associated.

Microscopic Examination: Section shows a large quantity of fibrinopurulent material. There is also some living fibrous tissue; although its surface cannot be seen, this is probably synovium. In it are numerous tubercle-like bodies consisting of giant cells, epithelioid cells and lymphocytes. The giant cells appear more like foreign body than like Langhans cells. There are extensive areas of necrosis of the muscle tissue.

Diagnosis. Tuberculosis of the gastrocnemius muscle (Figs. 3 and 4).

The presence of the tuberculosis within the knee joint aroused considerable doubt in the mind of the pathologist as to whether this should be considered a case of primary tuberculosis of the muscle, or whether it was secondary to the contiguous joint involvement. However, the appearance of the specimen at operation, the absence of any fistulous tract connecting with the knee joint, the fact that the proximal portion of the medial head of the gastrocnemius, for about $\frac{1}{2}$ inch beyond its insertion into the femur was grossly completely free of any tuberculous involvement, and the complete localization of the abscess cavity within the inner half of the gastrocnemius, would seem to justify the feeling that this is truly a case of involvement of the gastrocnemius muscle, independent of the tuberculous affection of the knee joint proper.

Though not commonly known, the clinical features of tuberculosis of muscle have been so well delineated by Bandelier and Roepke,[5] and later in greater detail by Zahnert (*loc. cit.*) that a brief recapitulation of their work may be condoned. All authors have been considerably exercised to account for the great infrequence of primary infection of muscle. Some have thought that this was due to the fact that tuberculosis is not prone to affect this highly differentiated tissue; others have believed that the reason lay in the relatively good circulation usually present in muscle. Still others have explained it as due to the presence of the normal muscle juices and the accumulation of lactic acid after function.

Muscular tuberculosis may occur at any age, but appears to be more common during the ages of 17 and 24. Males are more frequently affected than females. As noted above, the muscles of the extremities are more often involved than the muscles of the trunk. Injuries and excessive use, such as might be expected in men engaged in work, seem to predispose to the development of the condition.

Pathologically, the disease may be either of the typical giant-cell forming or of the endothelioid cell varieties. The vascular intima is for the most part the site of the localization of the tubercle bacillus. The interstitial connective tissue is first affected and the muscle tissue is only secondarily involved. Three main types have been described: 1, The tuberculous nodule; 2, the cold abscess; 3, the sclerosing interstitial myositis. To these have been added two other subdivisions; the fungus type and a pseudoneoplastic type observed in the abdominal muscles and corresponding in the main with a similar type of luetic infection elsewhere described.[6]

Clinically, the disease is extremely insidious and may remain unnoticed for a long time. Pain and fever are seldom seen. The general condition remains unaffected and attention is generally attracted to the condition by the appearance of a gradually enlarging swelling, which slowly becomes elongated in the direction of the muscle fibers. It is situated beneath the deep fascia and the skin over it is freely movable. As in other muscle tumors, the mass can be moved across the direction of the muscle fibers, when the muscle is relaxed, but becomes fixed upon contraction. The process is usually well encapsulated and seldom involves the surrounding structures, though different muscles may be involved at the same time. Because of its deep situation, the skin over the mass is never perforated and retains its normal color and texture.

The appearance of a normal skin overlying a definite tumor of muscle in a patient already afflicted with tuberculosis must arouse the suspicion of tuberculosis of the muscle. Differentiation must, of course, be made between this condition and the other types of muscle tumor occasioned by true neoplasms, parasitic disease, teratomata and inflammations, either of the acute, pyogenic type, or that due to the chronic granulomatous infections.

In the sense that tuberculosis of muscle is not known to lead to generalized tuberculous infection, the prognosis is good. On the other hand, spontaneous cure has never been observed. The treatment of choice is by excision of the affected muscle. Incision and curettage of the lesion has been advised, but is not to be recommended. Where the location of the disease is such that excision is impossible, the use of Bier's hyperemia, aspiration and injection of the cavity by means of 10% iodoform in glycerin, and Roentgen ray therapy have been used with satisfactory results. As in all forms of tuberculosis, the general care of the patient is a matter of prime moment.

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BOOK REVIEWS AND NOTICES.

SPINAL ANESTHESIA. Technic and Clinical Application. By GEORGE R. VEHRS, M.D., Salem, Oregon. Pp. 269; 81 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $5.50.

THE author states that this work, dedicated to the late J. C. Da Costa, constitutes a survey of the experimental and clinical records in the field of spinal anesthesia for the past 49 years. The style in this monograph is not an easy one, many of the chapters having been written in a choppy manner. In numerous instances the historical data are not correct. The author states "light and heavy novocain fluids, long used by Babcock" when it is well known that Babcock used stovain for many years. Ferguson is repeatedly spelt Furguson. In numerous other particulars the work falls short of the Reviewer's anticipations. Statements such as "the blood sugar immediately began to pyramid, with the greatest velocity in the first eight to ten hours" after ether anesthesia can hardly be true, since anyone who is at all familiar with the subject well knows that, although there is a marked rise in the blood sugar immediately after ether anesthesia is begun, there is a fall to nearly normal within a short time after recovery from the anesthetic. The work of Austin and his coworkers shows that acidosis is not a serious factor, as is here stated, in ordinary ether anesthesia. Nor is the statement that "in ether anesthesia, the poisons are generated by the destructive metabolic processes which limit the ability of body cells to utilize the blood sugar," a clear statement of the metabolic changes that occur in ether anesthesia. Spinal anesthesia needs no defense that is based on misstatements of the effects of other anesthetics, and the author's monograph would have been greatly improved had he avoided such pitfalls. The illustrations are excellent, and much of the practical discussion is interesting and valuable. In too many instances the author has, however, included clinical data which add little to the work and in some instances even show a failure critically to evaluate scientific material. For those who desire a reference book on spinal anesthesia this book will fill a need. The author states justly that "the greatest safety to the life of the patient in spinal anesthesia lies in specialization in technic by surgeons under experienced tutors. When dealing with human lives there is little room for the unexperienced." I. R.

ACUTE INTESTINAL OBSTRUCTION. By MONROE A. MCIVER, M.D., Surgeon-in-Chief, Mary Imogene Bassett Hospital, Cooperstown, N. Y. Pp. 430; 62 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $7.50.

THIS excellent monograph is divided into three major divisions: Part I, giving a general picture of the disease; Part II, dealing with diagnosis and treatment; and Part III, covering experimental work. There are in all 34 chapters, each followed by an excellent bibliography. The illustrations are good. The style is so smooth and the text so interesting that the Reviewer found himself reading it as he would an interesting novel. The author has thoroughly covered the historical aspects of each topic which he reviews. His clinical deductions are sound and the experimental aspects of intestinal obstruction are reviewed in a brilliant manner. He has been most modest of his own contributions to this very important field.

He has carefully covered the high and low obstructions and the common and uncommon causes of obstructions. He has in an unbiased manner carefully weighed the evidence as to the cause of death in the various types of lesions and has evolved from the best available sources the most rational methods of treatment. He has sanely evaluated the experimental investigations into this subject and has shown that much of this work can be directly applied to clinical practice. But the Reviewer must not say too much, for there is not a surgeon who can afford to be without this volume. I. R.

SURGERY OF A GENERAL PRACTICE. By ARTHUR E. HERTZLER, M.D., Chief Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas, and VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 602; 472 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $10.

THE basis of this book is the last edition of the senior author's *Minor Surgery* (1930), but the work is so completely rewritten that its origin could hardly be recognized. The three parts deal with "Special Surgery," "Regional Surgery" and "General Surgical Considerations." In all there are 31 chapters, well illustrated and, to a large extent, written in the inimitable Hertzler style. It may be questioned whether many of the subjects covered belong in a textbook covering the surgery of a general practice, but one can hardly say what is and what is not "minor surgery." The authors state that "those who shy at state medicine may serve the cause best by serving the patient efficiently, inexpensively and quickly. When the general practitioner cared for the ailing public, there was no complaint about the high cost of hospital care." This book will rapidly find its way into many bookshelves which already contain numerous volumes on similar subjects. It justly deserves this recognition. I. R.

MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC GUIDE. By JACOB GUTMAN, M.D., PHAR.D., F.A.C.P., Consulting Physician, Manhattan General Hospital, etc. Pp. 1393. New York: Paul B. Hoeber, Inc., 1934. Price, $7.50.

THIS tremendous book attempts to bring within one cover details of 8160 "popular" drugs of known and unknown composition, together with therapeutic information (396 pages) from three points of view: (1) Preparations classified chemically and pharmacologically; (2) preparations used in 16 specialties; and (3) diseases and the preparations indicated in their treatment.

Suffering from the unavoidable handicaps of such an approach, this book, like others of its type, betrays its limitations, even its traps, when one tries its use in a familiar field. As an up-to-date source of considerable information presented "without bias or comment," it has a distinct field of usefulness; it should not be used (and perhaps was not so intended) as a guide in the treatment of disease. A 60-page bibliography is a notably useful feature which makes its various parts readily usable.

E. K.

COCCIDIA AND COCCIDIOSIS OF DOMESTICATED, GAME AND LABORATORY ANIMALS AND OF MAN. Monograph No. 2, Division of Industrial Science, Iowa State College. By ELERY R. BECKER, D.Sc., Associate Professor of Protozoölogy, Iowa State College. Pp. 147; 25 illustrations. Ames, Iowa: Collegiate Press, Inc., 1934. Price, $2.50.

APPRECIATION of the economic importance of coccidiosis as a disease of domestic, game and laboratory animals is mainly the result of investigations

completed within the past few years. This monograph is a timely analysis of published material. The first chapter gives a general account of coccidia and coccidiosis. The next 22 chapters (all very brief) contain discussions of the disease in various animal hosts. An appendix of three sections gives references to species not mentioned in the text, a host catalogue and notes on technique. There is also an extensive bibliography. Authors and subjects are indexed separately. Those who are directly or indirectly interested in coccidia or in animals parasitized by them should find this book helpful. H. R.

TREATMENT IN GENERAL PRACTICE. By HARRY BECKMAN, M.D., Professor of Pharmacology at Marquette University School of Medicine, Milwaukee. Pp. 889. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, $10.

THOROUGH revision, the inclusion of some new material, the deletion of some of the old—in all of which the author shows an increasing and sound conservatism—combine to make the new edition an even better book than the first and highly to be recommended to all physicians. R. K.

TREATMENT OF THE COMMONER DISEASES. By LEWELLYS F. BARKER, M.D., Professor Emeritus of Medicine, Johns Hopkins University; Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 319. Philadelphia: J. B. Lippincott Company, 1934. Price, $3.

BASED upon ten post-graduate lectures to the Academy of Medicine of Lima and Allen Counties, Ohio, this volume deals "with the management of some of the internal disorders that are not infrequently met with by the physician who engages in general practice." The author states "I shall make no attempt to discuss fully and completely any topic whatever; but I shall feel free to wander whither I will, making running comments upon any subject that may occur to me as being pertinent to general medical practice." The author's rich experience, sound judgment and delightful style combine to make this little book valuable "brush-up" reading for the busy practitioner. A further feature is the large number of references (over 600) to original sources. The Reviewer, however, permits himself to differ with the recommendation to give quinine intravenously to patients who have an idiosyncrasy to quinine by mouth, as well as with that to use vigorous salvarsan treatment in syphilis of the liver. R. K.

NEW BOOKS.

The Surgical Clinics of North America, Volume 14, No. 3 (Mayo Clinic Number—June, 1934). Pp. 221; 70 illustrations. Philadelphia: W. B. Saunders Company, 1934.

Collens System of Diet Writing. Including Diet Calculator, Obesity Chart, 100 Menu Prescription Forms. By WILLIAM S. COLLENS, B.S., M.D., Chief, Diabetic Clinic, Israel Zion Hospital; Assistant Physician, Greenpoint Hospital; Metabolist, Brooklyn Women's Hospital; Consulting Metabolist, Rockaway Beach Hospital. New York: Form Publishing Company, 1934. Price, $5.

German Medicine. By W. HABERLING, M.D., Professor of The History of Medicine, Academy of Düsseldorf. Translated by JULES FREUND, M.D., Ex-Associate in Bacteriology, University of Pennsylvania. Vol. 13 of Clio Medica. Pp. 160; 9 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $1.50.

Medicine in Persia. By CYRIL ELGOOD, M.D., M.R.C.P., Late Physician to the British Legation, Teheran, Persia. Vol. 14 of Clio Medica. Pp. 105; 11 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $1.50.

Lane Medical Lectures: Biochemical Studies of Nutritional Problems. Vol. 3, No. 2 of Stanford University Publications. By J. C. DRUMMOND, Professor of Biochemistry, University College, University of London. Pp. 106; 6 figures. Stanford University, California: Stanford University Press, 1934. Price not given.

The Spastic Child. A Record of Successfully Achieved Muscle Control in Little's Disease. By MARGUERITE K. FISCHEL. Pp. 97; 2 illustrations and 14 figures. St. Louis: The C. V. Mosby Company, 1934. Price, $1.50.

The Laboratory Notebook Method in Teaching Physical Diagnosis and Clinical History Recording. By LOGAN CLENDENNING, M.D., Professor of Clinical Medicine in the University of Kansas. Pp. 71. St. Louis: The C. V. Mosby Company, 1934. Price, 50¢.

Médecine et Éducation. By G. MOURIQUAND, M. PÉHU, P. BERTOYE, J. BARBIER, P. VIGNARD, P. MAZEL, ABBÉ MONCHANIN, R. P. CHARMOT, and P. D'ESPINEY. Groupe Lyonnais d'Études Médicales, Philosophiques et Biologiques. Pp. 234; 1 illustration. Lyon: P. Lavandier, n.d. Price, 12 fr.

Craniocerebrale Schemata für die roentgenographische Lokalisation. By PROFESSOR DR. A. SCHÜLLER, Consiliarius am Zentral-Roentgen-Institut des allg. Krankenhauses in Wien (Leiter Dozent E. C. MAYER), and DR. H. URBAN, Assistent der psychiatrisch-neurologischen Universitätsklinik in Wien (Vorstand Prof. DR. O. PÖTZL). Pp. 8; 17 illustrations and 1 cellophane sheet. Leipzig: Franz Deuticke, 1934. Price, M. 4.

Die Ophthalmologie des Suśruta. Textkritisch bearbeitet, übersetzt und mit Concordanztabellen zu Bhāvamiśra versehen. By DR. MED. ET PHIL. A. ALBERT M. ESSER, Augenarzt in Düsseldorf. Heft 22 of Studien zur Geschichte der Medizin. Pp. 83. Leipzig: Ambrosius Barth, 1934. Price, Rm. 7.50.

NEW EDITIONS.

An Introduction to Practical Bacteriology. A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh, etc., and J. E. MCCARTNEY, M.D., D.Sc., Director of Research and Pathological Services, London County Council, etc. Pp. 504. Fourth edition. Baltimore: William Wood & Co., 1934. Price, $4.

Manual of the Diseases of the Eye. By CHARLES H. MAY, M.D., Director and Attending Surgeon, Eye Service, Bellevue Hospital, New York, 1916 to 1926; Consulting Ophthalmologist to the Mt. Sinai Hospital, to Bellevue Hospital, to the French Hospital, New York, and to the Monmouth Memorial Hospital, etc. Pp. 496; 376 illustrations including 25 plates with 78 colored figures. Fourteenth edition, revised. Baltimore: William Wood & Co., 1934. Price, $4.

This manual for students and practitioners continues its successful course.

Applied Physiology. By SAMSON WRIGHT. Pp. 604; 195 illustrations and 1 colored plate. Fifth edition. New York: Oxford University Press, 1934. Price not given.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

THE PATHOLOGY OF PNEUMONOCONIOSIS: A REVIEW.

SIXTY-SEVEN years ago Prof. Kussmaul, of Freiburg in Breisgau, wrote: "The inhalation of dust particles as a disease-producing potentiality has, with good cause, greatly occupied the medical profession in the last two hundred years, as witness of which there is to be found a large series of excellent treatises by English, French, German and Belgian physicians, dealing with diseases of labouring classes whose occupations compel them to work in dusty air." If, in Kussmaul's time, there was already a large series of treatises on the subject, how may the present-day mass of literature be represented?

The many contributions of recent years have attacked the problem from various angles, and none with greater effect perhaps than those which have dealt with the pathogenesis of the disease; for upon an elucidation of the underlying morbid process awaits the hope of therapy and prevention. It is in consequence of a current tendency to question some of the older conceptions of the pathology of dust diseases that the need for a review arises.

Though, broadly speaking, all occupations involving habitual exposure to dusty atmospheres have been attended by some menace to health, attention has been gradually focused more acutely on those industries in which the workers suffer from a high incidence of pulmonary phthisis; and the more offensive dusts have been gradually singled out, until of late years the incriminating finger of scientific scrutiny points almost exclusively to one common constituent of the earth's crust, namely, silica, as the chief if not the only source of the phthisis-producing dust of industry.

The evidence against silica is based largely upon studies of vital statistics, such as have been made by Collis (1915, 1919, 1921, 1933), Middleton (1919), Greenburg (1925), Stewart (1929), Russell (1930), Policard and Martin (1930), and the credibility of the evidence rests upon the demonstration that uncombined silica (SiO_2) comprises or is a constituent of nearly every dust concerning which vital statistics display a high death rate from phthisis among the affected peoples.

Of late, however, doubt has arisen in several quarters as to the accuracy of attaching all the blame to silica. It has been seriously

questioned whether some other mineral substances may not also give rise to dangerous dusts in industry; whether, in fact, the disease entity which has come to be more or less universally recognized as silicosis may not be due, in some instances at least, to the inhalation of dusts which contain no uncombined silica. With the idea, therefore, of seeking to avoid misapplication of the term silicosis to disease processes possibly not caused by silica, the more comprehensive term pneumonoconiosis (coined by Zenker, in 1866, meaning literally "lung full of dust") will be used wherever possible in this review.

It will not be amiss to summarize briefly the tissue changes which characterize pneumonoconiosis. These have been well described by numerous authorities. (Greenhow, 1865, 1866, 1867, 1869; Zenker, 1866; Arnold, 1885; Ziegler, 1908; Shattock, 1914; Watkins-Pitchford, 1914, 1915, 1927; Watt, Irvine, Johnson and Stewart, 1916; Middleton, 1919; Landis, 1919; Mavrogordato, 1922, 1926; Kettle, 1925, 1933; Cummins, 1927, 1931; Ickert, 1928; Schridde, 1929; Gardner, 1929; Strachan, 1930; Simson, 1930; Strachan and Simson, 1930; Irvine, Simson and Strachan, 1930; Giese, 1931; and Leporin, 1931.) Up to a certain point, all the common inorganic dusts, when inhaled in appreciable quantities over long periods, produce remarkably similar effects upon the lungs.

The Phases of Pneumonoconiosis. The initial insult is felt by the lining membranes of the air passages. Collis (1915), who has dealt fully with this phase of the reaction, asserts: "Bronchitis is, *par excellence*, the chief of the pneumonoconioses"; and Strachan and Simson emphasize the presence of a dry bronchiolitis from the start. Nearly all authors stress the persistence of a bronchitis throughout the course of the disease; and, save to mention that it varies in severity from one type of dust to another, it need not occupy our attention further.

Gardner (1933) describes 5 phases of the reaction, which, with slight modifications to fit the terminology of other writers and combining his 3rd and 4th phases under one heading, will serve as a basis upon which to summarize the main reactions.

1. *Early Parenchymatous Lesions.* When appreciable quantities of dust first permeate the air sacs many phagocytes wander out from the alveolar walls to ingest the particles and a state of catarrhal inflammation is set up. If the dust be particularly irritant or accompanied by pathogenic organisms, a sharp inflammatory process in the form of a bronchopneumonia may supervene. This is commonly what happens in experimental animals during dusting experiments, and with them the pneumonia often proves fatal. If they survive such an attack, patches of the pneumonia commonly fail to resolve, and plugs of exudate containing many dust-laden phagocytes undergo organization and form balls of cellular fibrous tissue within alveolar ducts and atria. Such lesions have often been misinterpreted as constituting "silicotic nodules," an error which vitiates some of the experimental work to be considered later. In the absence of pneumonia, or following its subsidence, the lung attempts to rid itself of dust-laden cells within the air sacs. Phagocytes which are grossly overloaded with foreign particles, and having little ameboid activity, are slowly evacuated into the bronchioles, carried up by the ciliary action of the bronchial mucosa and finally expectorated. More active phagocytes penetrate the alveolar walls and gain access to the lymphatic channels within the interstitial framework of the lungs.

2. *Lymphatic Stasis.* At this stage pneumonoconiosis becomes essentially a disease of the pulmonary lymphatic system, a chronic, obstructive lymphangitis of the lungs. In order to grasp the significance of this condition it is necessary to understand the anatomy and function of the pulmonary lymphatic drainage as described by Arnold (1880), Miller (1911), Haythorn (1913) and Simson (1930). Briefly, the lymphatic system of the lung consists of a series of irregular and ill-defined channels in the subpleural and interlobular connective tissues and in the adventitial coats of bloodvessels and bronchi; these channels are equipped with rudimentary valves (Dunham, quoted by Landis, 1919); they converge at the hilus and drain into the tracheobronchial glands. A sharp distinction should be made between lymphatic channels and lymphoid tissue; the latter constitutes lymph nodes which act as traps or filters along the course of the channels. Small lymph nodes are present in the pleura and along the bronchi, becoming larger and more numerous toward the hilus, where they merge with the tracheobronchial and mediastinal glands. To the pulmonary lymphatics belongs the important function of providing an exit from the lung for phagocytes laden with foreign particles or microörganisms, and they also serve a significant purpose in the resolution of inflammatory processes (Haythorn, 1913).

As dust is evacuated from the lung *via* the lymphatic route it piles up in the nodes, which soon become congested to such a degree that they develop a diffuse hyperplasia of their reticular cells amounting to a fibrosis, in which the dust particles are more or less permanently incarcerated (Herring and McNaughton, 1922). Then stasis develops in the afferent lymphatic channels and gradually spreads farther and farther afield, until the lung is streaked and mottled with dust collections. This is not necessarily a permanent state of affairs (Haynes, 1926). Given rest from further exposure, much of the dust in the afferent channels may be removed (Mavrogordato, 1926), or if edema supervenes, the dust-laden phagocytes may be reactivated and migrate bilusward or backward into the air sacs again (Haythorn, 1913). In the event of continued inhalation the lymphatic channels eventually become congested and choked with dust-laden phagocytes. The phagocytes tend to break down and the liberated particles are transferred to reticular cells, which increase in number and give rise to a moderate permanent thickening of the connective tissues in the pleura, interlobular septa and adventitial coats of bloodvessels and bronchi. When examined microscopically, sections from such a lung show the bloodvessels and, to a lesser extent, the bronchi and bronchioles (Haynes, 1926) mantled with a coat of dust-laden reticular cells, often enclosing small channels filled with dust-laden phagocytes, collections of which Mavrogordato likens to thrombi. Similar deposits of pigment may be seen immediately under the pleura and in the interlobular partitions, but not in the alveolar walls (Simson, 1930). The vessels are not affected by the surrounding dust and fibrosis. One or two authors have described an endarteritis obliterans in relation to pneumonoconiosis, but others have shown that it does not occur. With most inert foreign materials, the commonest example of which is coal dust, this is the sum total of the reaction. Landis (1919) points out that lymphatic pneumonoconiosis of mild degree is present to some extent in nearly all adult city dwellers, but rarely interferes with health. Mavrogordato

(1926) observes that the pulmonary lymphatics may be occupied for years, even by a so-called phthisis-producing dust, without provoking clinical signs or appreciable fibrosis.

3. *Perilymphatic Fibrosis and Beading.* With the more injurious dusts additional changes commonly take place. The interstitial tissues with which the dust is in contact begin to thicken and nodular aggregations occur at the points of junction of various lymph channels where small receptacula are formed, particularly where the interlobular septa join the pleura and where the bronchi and bloodvessels bifurcate. These aggregations constitute the "pseudotubercles" of Mavrogordato (1922) and the "intralymphatic plaques" of Carleton (1924) and the "beading" commonly referred to by roentgenologists. Mavrogordato observes "the pigment-bearing cells accumulate at certain points (along the lymphatics), bringing to mind 'log jams' at the turns and shallows in rivers of a lumber country." Groups of dust-laden cells collect in these plaques and lay down a fine network of reticular fibrils (Gardner, 1932), thus giving rise to a permanent lesion (Carleton, 1924), which, however, does not yet constitute the so-called "silicotic nodule" to be considered presently. Mavrogordato (1922) has suggested the term "lymphatic cirrhosis" of the lung as applicable to this phase of pneumonoconiosis. It should be emphasized that up to, and including this stage, the parenchyma of the lung is as yet uninvolved by any permanent change. Though beading of the linear lymphatics is regarded as positive evidence of a pneumonoconiosis from the standpoint of compensation, the discrete, parenchymal nodules, held to be specific for silicosis, are as yet lacking.

The gross appearances of the lung at this stage of pneumonoconiosis are characterized by excessive pigmentation, for, whatever be the essential nature of foreign particulate matter within the lung, it is always of a mixed character and contains colored matter in the form of carbonaceous or argillaceous particles or both. Pigmentary injection of the pulmonary lymphatics shows itself then to the naked eye as marbling of the pleura, streaking and mottling of the cut lung surface and uniformly deep coloring of the tracheobronchial glands. Watkins-Pitchford (1915) aptly states that, unless at least some excess of pigmentation is found in the substance of the lung, it may be safely concluded that the individual was not the subject of pneumonoconiosis in any form. The pigmented moiety of the inhaled dust is not necessarily the mischief-making factor, nor is it always increased in proportion to the amount of damage present, nor does it necessarily indicate excessive exposure to pigmented dust, for it may simply represent the usual anthracotic pigmentation common to the lungs of nearly all adults, but somewhat increased as the result of faulty elimination due to choked lymphatic exits (Watkins-Pitchford, 1915). Another distinctive feature of simple pneumonoconiosis is that the tissue changes are symmetrical and uniform throughout both lungs, a feature which, theoretically at least, distinguishes the simple from the complicated pneumonoconiosis.

With the proliferation of reticular cells, and ultimately the laying down of collagen in relation to the dust deposits, the lesions become definitely demonstrable to the touch, a factor of paramount importance in a legal sense, for in most countries it is only when the lesions are both visible and palpable that the presence of silicosis in a lung speci-

men becomes recognizable by law (Watkins-Pitchford, 1927). On the cut surface of such a lung the dusted foci may, therefore, stand out as palpable nodules, whereas in reality they are not nodules at all, but simply the cut ends of thickened lymphatic trunks with bloodvessels or bronchi in their centers. Watkins-Pitchford has shown (1915) that, when dissected out, these palpable lesions are really beaded strings and not discrete nodules. There has been much confusion occasioned in the minds of many investigators by failure to differentiate this simple lymphatic thickening from the more specific, discrete, so-called "silicotic nodule," to be considered presently.

The tracheobronchial lymph nodes are densely pigmented, usually jet black, a little enlarged and of rubbery consistency. Microscopically they show a heavy deposition of dust particles in the reticular cells. Fibrous nodules are not necessarily present in the nodes; the usual type of induration consists of a more or less diffuse hyperplasia of reticular cells, more marked in the medulla than in the cortical parts of the gland.

4. *The Stage of Nodulation ("Silicotic Nodule").* In the more serious types of pneumonoconiosis, notably in silicosis, there occurs a characteristic lesion of a sort quite different from the lesions described up to this point. It consists of a dense nodular growth of connective tissue formed of more or less concentric strands of collagen, sometimes forming a filigree pattern, always interlarded with narrow chinks like basketwork, always acellular in the central portions and invariably surrounded by a zone of cellular connective tissue. These nodules occur singly, in which case they are quite small, averaging about 1 mm. in diameter, but more commonly they are agminated into small composite groups of the size of a pea or occasionally somewhat larger. They are found in the parenchyma of the lung, in the subpleural tissues and in the hilus glands. Their distribution is characteristic; they always appear to arise in interstitial tissue of the lung (Mavrogordato, 1922), commonly at the entrance to the lung lobule (Simson, 1930; Irvine, Simson and Strachan, 1930), though not necessarily in relation to lymphoid tissue (Kettle, 1932). They stand discrete from bloodvessels or bronchi. Quite often composite nodules appear to replace entire lung lobules (Zenker, 1867; Watkins-Pitchford, 1914, 1915; Belt, 1929). Not infrequently, composite nodules are so thickly placed as to form a massive induration, replacing large areas of lung parenchyma. The nodules are of firm, rubbery consistency and iron-gray to black in color. The larger nodules often have a laminated appearance demonstrable to the naked eye and show thin rings, like the annual rings of a tree trunk; the intensity of the pigmentation varies from one ring to another so that it is not uncommon to find one or more rings of pale silvery color in an otherwise black nodule. In an area of conglomerate nodules these rings of lesser pigmentation lend to the specimen a peculiar naked-eye appearance which Watkins-Pitchford (1915) has designated as "fibrotic figures." On the whole, the nodular lesions are much less deeply pigmented than the perivascular and peribronchial aggregations. In distribution the nodular lesion tends to be much more irregular than the changes of the preceding phase of the reaction. It is usual to find some parts of the lung less affected (by the nodular lesion) than others; indeed, there may be only 1 or 2 nodules in a single lobe or in a whole lung (Watkins-

Pitchford, 1915). In the tracheobronchial glands the nodular lesions tend to localize in the cortex, near the capsule (Giese, 1933), in contrast to the diffuse fibrosis of the second and third phases, which has a predilection for the hilus of the gland.

The nodular lesions are of more serious consequence than the relatively innocuous lymphatic cirrhosis of simple pneumonoconiosis. The economy of the lung now suffers interference. Considerable areas may be consolidated as the result of massive fibrosis, and, while this in itself is seldom sufficient to produce death, yet emphysema and embarrassment to the right side of the heart are common sequelæ and not infrequently determine a fatal issue. But what is of greater consequence, the individual is now a very poor risk, should pulmonary infection supervene.

The Nature of the "Silicotic Nodule." Concerning this nodular lesion pathologists are unanimously agreed that it is of more or less constant morphologic character and peculiarly distinctive of full-blown pneumonoconiosis. But here the unanimity ceases; as to the exact etiology, pathogenesis and significance of the lesion there is great divergence of opinion. The majority of pathologists have followed in Zenker's footsteps and regarded it as a lesion produced entirely through the agency of dust. Many have taken the further step of ascribing it specifically to silica dust, and consequently it has come to be known the world over as a "silicotic nodule." A few have clung to the alternative idea which was also in Zenker's mind, that it represents an obsolete tuberculous process; others regard it as a combined effect of tuberculous infection plus excessive dust inhalation.

Were it not for the fact that pulmonary tuberculosis so often complicates pneumonoconiosis, the problem of deciding the etiology of the silicotic nodule would be simplified. But the two diseases are so frequently coupled in industry that the question of the respective rôle of each has been a notoriously perplexing problem.

There is the incontrovertible fact of a high incidence of nodular pneumonoconiosis in individuals whose occupations expose them to the inhalation of large quantities of silicious dust. It has been shown also that the silicotic nodule often contains appreciable numbers of silicious dust particles (Greenhow, Zenker, Watkins-Pitchford, Collis, Mavrogordato, Belt, Giese, Gardner, Klotz, *et al.*), a fact which suggests an etiologic relationship of the dust to the lesion. On the side of negative evidence in the same direction, stress has been laid on the consistent absence of histologic criteria of tuberculosis in the silicotic nodule; where there are neither giant cells nor caseation nor characteristic granulomatous reaction, most morphologists refuse to recognize the elements of tuberculous infection. Numerous attempts to demonstrate the tubercle bacillus in the silicotic nodule have failed, and in a few instances where biologic tests have been carried out, the tissues have proved negative on guinea-pig inoculation (Strachan and Simson, 1930). Furthermore, there comes from all sides the common clinical observation that many cases of nodular pneumonoconiosis fail to evince the signs and symptoms of an infective process.

Numerous attempts have been made to reproduce the lesions of pneumonoconiosis by the introduction of various types of dust into the tissues of experimental animals. (Ruppert, 1878; Wainright and Nichols, 1905; Beattie, 1912; Cesa-Bianchi, 1913; Mavrogordato,

1918; Gardner, 1920 *et seq.;* Gye and Purdy, 1922; Carleton, 1923; Rona, 1924; Willis, 1928; Mills, 1931; Haynes, 1931; Policard, 1931; Policard and Rollet, 1931; Kettle, 1932, 1934; Lemon and Higgins, 1932; Lemon and Feldman, 1933; Cameron and Lang, 1933; Miller and Sayers, 1934; Robson, Irwin and King, 1934.)

These experiments have proved of great value in elucidating the cytology of the dust reaction and ascertaining the relative effects of various dusts, and, while for the most part little difficulty has been experienced in reproducing the early lesions of pneumonoconiosis as seen in man, *viz.*, lymphatic choking and thickening, plaque and pseudotubercle formation, yet the results have been singularly disappointing as regards reproduction of the well-known silicotic nodule of the human disease. Many authors have claimed experimental reproduction of "typical silicotic nodules," but careful scrutiny of their illustrations and descriptions fail to convince one that their claims are valid. Nearly all experimentalists in the field of pneumonoconiosis stress the high incidence of pneumonia in dusted animals, and, from a critical evaluation of their results as a whole, it seems more than probable that the majority of fibrous lesions produced in the parenchyma of animals' lungs by experimental dusting are due in no small measure to a secondary pneumonia rather than to the dust *per se*. Thus, in the latest piece of experimental dusting to be reported (Robson, Irwin and King, 1934), the lesions claimed to be "typical, silicious, fibrotic nodules" are obviously nothing more than patches of organized pneumonia, bearing no resemblance either in morphology or distribution to the silicotic nodules of a miner's or a stonemason's lung. Strachan (1930) expresses grave doubt as to whether a true, non-infective, uncomplicated silicosis (meaning the nodular type) has yet been produced in experimental animals. The same doubt is expressed by Kettle (1934). Researchers who have injected dust suspensions intravenously or subcutaneously have produced quite definite lesions, usually ending in fibrosis, but it is not too much to say that none of these has reproduced the silicotic nodule.

The prolonged and elaborate experimental work of Gardner (1932) stands out in contrast to the rest as having attained results more comparable to the human lesions. In the lungs of some of his rabbits and guinea pigs exposed to daily dusting with particulate silica and silicates for periods up to 3 years and more, there have developed fibrous nodules quite like the fibrous knots of human pneumonoconiosis, though still falling somewhat short of exact duplication. Gardner himself admits there is at least one peculiarity of his experimental nodules, namely, that they remain vascularized, which makes them differ from their human counterpart.

With this long series of experiments in the background illustrating the difficulty of reproducing the silicotic nodule, the recent successful attempt by Kettle (1934) is particularly significant. By the addition of dead tubercle bacilli to a suspension of powdered clay (aluminium silicate), the characteristic lesion was induced in guinea pigs' lungs in the relatively short period of 112 days. The illustrations accompanying Kettle's report leave no room for doubt that the silicotic nodule has at last been faithfully reproduced. The significance of Kettle's work lies, of course, in the fact that it strongly suggests the silicotic nodule to be the result of the combined effect of a dust factor plus

a tubercle factor. This bit of experimental evidence lends strong support to a view which has long been in the back of many an investigator's mind and openly expressed by not a few. Watkins-Pitchford at first (1914) took the silicotic nodule for a non-infectious lesion due solely to dust, but later (1915) he says "I now think I may have been mistaken and that these fibrotic figures, though histologically totally dissimilar to tubercles, are a pathologically unique indication of the presence of the tubercle bacillus in the silicotic lung. . . . Dr. L. G. Irvine has long held that these peculiar gray figures were due to a tuberculous infection. . . . Isolated examples of these figures are sometimes seen to be the seat of caseation, organisms have occasionally been found in them and biological tests of their contents are sometimes positive for B. tuberculosis." Policard (1930) says "In the immense majority of cases, if not in all, the silicotic lung is also a tuberculous lung." Irvine, Simson and Strachan (1930) make the following significant statement: "We should not think of 'simple' silicosis merely as a dust fibrosis, but as being, at least in many cases, a dust fibrosis, which from its beginning as a clinically detectable condition is linked up with an element of latent tuberculous infection." In the same article as the above quotation appear the following striking figures as to the prevalence of tuberculosis among silicotic miners in South Africa: 1923 cases were diagnosed as primary "simple" silicosis from 1917 to 1923. Of these, 543 were dead by July 31, 1929, 373 having died of tuberculosis. And Professor Loriga, of Italy (1930), adds "The infectious tubercular factor constitutes such a frequent complication as to leave the doctor almost constantly in doubt in regard to the gravity of the pneumonoconiosis considered as a separate disease."

It is questionable whether those who regard or have regarded the silicotic nodule as a dust lesion (Zenker, 1867; Beck, 1895; Shattock, 1914; Watkins-Pitchford, 1914; Collis, 1915; Mavrogordato, 1922; Cummins, 1927; Gardner, 1929; Bergstrand, 1930; Böhme, 1930; Schridde, 1929; Strachan and Simson, 1930; Giese, 1931 and 1933) have justifiably ruled out tuberculosis because of the lack of giant cells, caseation and typical granulomatous reaction; for an obsolete tubercle commonly shows none of these features and surely the obsolete lesion is just as typical of tuberculous infection as the active lesion; for do not the great majority of tuberculous lesions tend to heal? Obsolete miliary tubercles of the spleen and liver are relatively common autopsy findings (Klotz, 1917) and show morphologic characters quite similar to silicotic nodules except that they contain no dust particles; but one point that the above-mentioned authors have been hard pressed to explain is the relative paucity of dust particles in the silicotic nodule. Watkins-Pitchford and Moir (1916) found by a delicate histochemical test that there was little or no foreign particulate matter in certain massive areas of nodular fibrosis in silicotic lungs and concluded that the lesions in question were, therefore, due to infection rather than to dust. As one who at first championed the silica specificity of the silicotic nodule, the reviewer (Belt, 1929) has since had cause to doubt whether certain fibroid lesions of ordinary obsolete tuberculosis could be distinguished from silicotic nodules except by reference to the occupational history of the case. This comes from a wider acquaintance with the pathology of uncomplicated tuberculosis. No

one will deny that the silicotic nodule differs from the ordinary run of healed tubercles, but the differences seem to represent only a modification of the usual process, in the direction of a more complete fibrosis, presumably caused by the presence of dust particles (Kettle, 1934).

Among others who adhere to the silica specificity of the silicotic nodule, Strachan and Simson (1930) claim to be able to trace the various steps in the development of the lesion in human cases from the simple aggregation of dust to the full-blown hyalinized knot of fibrous tissue. Their contentions are unconvincing. One palpable weakness of their presentation is that they fail to treat of the possible existence of such a thing as a healed, fibroid tuberculous lesion. The majority of lesions one sees in the pneumonoconiotic lung are either of a healed character or they are obviously tuberculous (Belt, 1929), and the various stages of development of the silicotic nodule are notoriously difficult of detection unless the nodule be construed to represent the end stage of the pneumonoconiotic tubercle, in which case the earlier phases of its development are often readily demonstrable.

If then, on the basis of this accumulated evidence one is prepared to admit that the silicotic nodule is really a healed tubercle modified by dust, it means that all cases of pneumonoconiosis characterized by the formation in the lung parenchyma of fibrous nodules, single, conglomerate or agminated into masses (and this would take in the majority if not all clinically demonstrable cases), are complicated by tuberculous infection from the start. This is precisely the contention of Irvine (1930), Leporin (1931) and Policard (1933).

The Dangerous Dusts. Silica has long been impugned as the chief cause of industrial phthisis. The evidence against silica has been built up largely upon statistical evidence (see page 424), the reliability of which has been questioned by Landis (1919), Loriga (1930) and Kettle (1932), but accepted by most other authorities. There is also much experimental evidence to show that finely particulate, colloidal and soluble silica are capable of producing proliferative lesions in animal tissues (Gye and Purdy, Mavrogordato, Carleton, Mills, Gardner, Haynes, Kettle and Policard), but that the silicotic nodule has ever been reproduced experimentally is open to question (see page 430). In their analysis of the mineral content of silicotic lungs in South Africa, Watkins-Pitchford and Moir (1916) claim to have found 400 particles of quartz for every 1 particle of other substances. But silica is obviously not the whole story. Cummins (1931) has established the presence of silicosis among Welsh coal miners who have not been exposed to the dust of free silica, for the rock in which they work contains only silicates (Jones, 1933). Jones, who has investigated the mineral content of the lungs of some of these cases, believes the mischief is produced by sericite, a potassium-aluminium silicate, and sees grounds for regarding this substance rather than silica as the universal cause of silicosis. Haynes (1931) has shown by animal experimentation that flint, slate, aluminium hydroxid, precipitated chalk, magnesium carbonate, carborundum, wood charcoal and colloidal coal all produce proliferative lesions in guinea pigs' lungs indistinguishable from the early lesions produced by silica. Though the dust of clay (kaolin or aluminium silicate) has been pretty generally regarded as innocuous, Kettle (1934) has shown that it produces an active tissue response in guinea pigs' lungs, and by combining this

dust with dead tubercle bacilli he has succeeded in reproducing typical silicotic nodules (1934) (see page 430). Kettle (1934) also observes: "I have myself seen pleural drift, plaque formation and a moderate degree of fibrosis, that is, the accepted signs of an incipient pneumonoconiosis, with such an inert substance as carbon." Asbestos is a magnesium silicate containing little or no free silica yet capable of producing serious lung lesions both in man (Cooke, 1927; Gloyne, 1930; Sparks, 1931; Ellman, 1933) and in animals (Gardner, 1931; Schuster, 1931). The first case of pneumonoconiosis reported by Zenker (1867) was due to the prolonged inhalation (7 years) of powdered red oxid of iron. The anamnesis was carefully investigated and it was clear this patient had no unusual exposure to other types of dust, yet it is obvious from Zenker's illustrations that the lungs presented lesions which would now be regarded as typical silicotic nodules, except that they were red in color. Zenker regarded all types of pneumonoconiosis as essentially of the same nature, save that the color of the lesions varied with the type of dust involved. Greenhow (1869) described several cases of flaxdressers' pneumonoconiosis; he found the pulmonary lesions essentially the same as those of colliers', miners' and stonemasons' phthisis also examined by him, except that the flaxdressers' lungs contained less silica by chemical assay; and he concluded "The nature of the substance inhaled appears to be of secondary consequence as regards the ultimate result." Shattock (1914) says "Striking tuberculoid lesions are sometimes encountered (in the pneumonoconiotic lung) and the likeness is not determined by the particular kind of material inhaled." Haythorn (1923) claims all dusts are a menace to health if inhaled to excess. Collis (1915) lays down the general principle "That dusts are more injurious as their chemical composition differs from that of the human body." If one is justified in drawing any conclusions from this diversity of data and opinion, it would be to the effect that, though silica undoubtedly constitutes a serious health hazard, its specificity as a cause of pneumonoconiosis has probably been grossly overrated; that at least some of the silicates and possibly a few substances other than compounds of silicon are culpable to some degree.

The chemists have been not a little at fault in promulgating the idea of the specificity of silica in regard to pneumonoconiosis. There is no satisfactory test for the presence of silica (SiO_2). By chemical assay one can only detect the presence of silicon and cannot determine in what combination the element exists, whether as a silicate, as oxid of silicon or as silicic acid; but the universal custom is to express the result of the assay as so many milligrams of "total silica" per unit of dried tissue or per unit of the ash. Many people, unfamiliar with the meaning of "total silica," have erroneously taken it to represent the amount of actual silica present in a given specimen and have, therefore, attached undue etiologic significance to silica.

The Size of the Harmful Particles. By digesting the tissue with strong acid and recovering the mineral matter, Greenhow (1865), McCrae (1913), Watkins-Pitchford and Moir (1916), Cooke (1933) and Jones (1933) have studied the morphology of foreign particles in the pneumonoconiotic lung. These authors are in agreement that the majority of such particles are of the same order of size as common microörganisms. The average dimension is about 1.2 μ; particles larger than

12 μ have not been observed in the pneumonoconiotic lung with the exception of asbestos particles which, quite unlike other dusts, enter the lung in the form of unusually long fibers, sometimes 100 to 200 μ in length (Gardner, 1931). Particles this large do not, however, penetrate the tissue. Recently Gardner and Cummings (1933) have shown by an ingenious experiment that particles of quartz under 3 μ are much more productive of connective tissue proliferation (liver cirrhosis) than particles of larger size.

How Do the Dusts Act? There is ample evidence to show that dangerous dusts generally stimulate reticular cells to proliferate. The mechanism of this stimulation still awaits demonstration. The old view that the hardness and sharpness of the particles had something to do with provoking the reaction has long since been discarded. From the work of Haynes, Mavrogordato and Gardner, considerable importrance attaches to the reaction which the various dusts call out on the part of the phagocytes. Dusts which are more actively phagocyted are, in general, more readily eliminated from the lung, either by expectoration or by passage through the lymphatic exits to the hilus. Dusts which provoke only a sluggish reaction on the part of the phagocytes, notably stone dust (Lauche, 1930), tend to congest the lymphatic channels and to remain more or less permanently incarcerated in them. Mavrogordato states: "Dusts that make mischief are dusts that accumulate. Dusts that are eliminated are dusts that produce a marked initial reaction." And Haynes concludes, "The intensity of the initial reaction to a dust is in inverse ratio to the degree of eventual damage caused by the dust." Gardner believes that intimate contact between silicious dust and connective tissues eventually leads to proliferation of the latter. Against this contention we have the well-known fact stressed by numerous authors that large amounts of particulate silica may apparently remain for years in the human lung without provoking any appreciable reaction.

Of recent years many investigators have swung to the view that silica undergoes a slow dissolution in the tissues, thereby liberating a toxic substance which by its injurious effect upon reticular cells stimulates them into excessive, reparative proliferation. The work of Gye and Kettle has perhaps done most to promote this view; they first demonstrated the toxicity of soluble silica, then observed that powdered quartz produced the same effect but required a longer time; they presumed that in the interval part of the quartz had gone into solution. The reviewer (Belt, 1929) thought to have adduced evidence of the slow solution of silicious particles in the human lung, but has since come to question the validity of his earlier deductions. Working on the hypothesis that silica is soluble in the tissues, Heffernan has elaborated physicochemical theories to explain the injurious effect. But it may safely be said that the solubility of silica in the tissues has not yet been satisfactorily demonstrated (Gardner, 1932).

Perhaps the most deleterious *modus operandi* of dust is its action as a carrier or vehicle for pathogenic organisms, facilitating their entrance into the lungs (Landis, 1919), for the rôle of secondary infection is coming to be regarded as of greater importance than the rôle of dust *per se* in the production of pneumonoconiosis (Irvine *et al.*, 1930; Kettle, 1934). Mavrogordato (1926) makes the significant statement that the dust concentration may be an adequate measure of risk of pneumonoconiosis

when dust concentration is high, but it is not so adequate when dust concentration is low, as it is nowadays in most industries, for the factor of tuberculosis may be dominating the situation.

Haldane (1913), Mavrogordato (1922), Carleton (1923) and Haynes (1931) have assembled evidence that certain relatively innocuous dusts may forestall the evil effects of more harmful dusts if inhaled at the same time. For a discussion of this moot question the reader is referred to Kettle (*Brit. Med. J.*, 1932).

Factors Contributing to the Development of Pneumonoconiosis. The integrity of the upper air passages and the efficiency with which inhaled dust is filtered out before reaching the lungs is of great importance. Mouth breathers tend to develop pneumonoconiosis more rapidly than those who breathe through their noses (Watt *et al.*, 1916). Since pneumonoconiosis is primarily a disease of the pulmonary lymphatic apparatus, it follows that any preëxisting disorder of this apparatus predisposes to a more rapid development of the condition, given adequate exposure to dust. Gardner (1924) states that a subject whose pulmonary drainage is already impaired by chronic or healed tuberculosis of the tracheobronchial glands should develop silicosis more rapidly than one whose nodes are normal. Lanza (1933), while refusing to believe that individual susceptibility plays any appreciable part in the etiology of silicosis in otherwise normal individuals, stresses the importance of preëxisting lung disease, especially tuberculosis and incipient pneumonoconiosis other than silicosis, as the factor which tends to hasten and aggravate silicosis. Age is also a factor; according to the Picher studies (quoted by Lanza, 1933), those who started mining after 40 years of age had an average of only 7.83 years of employment. Lanza also states that Wassermann-positive individuals develop silicosis more rapidly than the Wassermann-negative group and their disease runs a more rapid course.

Duration and Progress of the Severe Pneumonoconioses. Pneumonoconiosis is generally regarded as a disease characterized by extreme chronicity. Most authors are agreed that it takes from 4 to 20 years' exposure to relatively heavy concentrations of dust; and that even longer exposure may fail to produce the disease. South African experience shows that, in the case of those affected, the mean duration of exposure before the disease is detected is about 12 years (Mavrogordato, 1930); that the average expectancy of life of a case of silicosis when first detected is 13.66 years; and that the average duration of the second stage is 7 years (Irvine, Strachan and Simson, 1930). There is great variation in progress from case to case, but in the majority the disease tends sooner or later to advance and continue to do so even after the victim ceases his dusty occupation.

A few examples have occurred of a rapidly progressive pneumonoconiosis which have been regarded and recorded as cases of acute silicosis (MacDonald, Piggot and Gilder, 1930; Chapman, 1932; Kilgore, 1932); but cases of this kind which have come to autopsy have proved to be instances of acute tuberculosis enhanced no doubt by the silica present (Kettle, 1932; Gardner, 1933). Gardner (1933) made a pathologic examination of 15 such cases and concluded: "Although there is histological evidence of silicosis, atypical in character, it seems doubtful whether there is justification for describing the process as acute."

It will be remembered that the majority of cases are considered to be infective from the beginning (see page 431), and Strachan and Simson (1930) express a generally accepted dictum when they say "All silicotics, if they live long enough, die of tuberculosis."

Pneumonoconiotic Tuberculosis. The combination of pneumonoconiosis and tuberculosis does not necessarily imply an acute and dramatic pulmonary tuberculosis (Kettle, 1934). The "infective" silicosis of South Africa is a slowly progressive lesion in which necrosis and fibrosis proceed hand in hand with a preponderance of the latter (Irving *et al.*, 1930). Landis (1919) says that tuberculosis commonly runs a latent and more prolonged course in silicotics than in ordinary hospital patients, and Collis in his comprehensive review (1915) mentions that some authorities claim tuberculosis, when implanted on silicosis, progresses more slowly than ordinary tuberculosis, though he himself was of the opposite opinion. Gardner (1924) found that the course of a primary inhalation infection with virulent tubercle bacilli (in guinea pigs) becomes more chronic as a result of subsequent inhalation of granite and carborundum dust; the death of the animal is postponed and the pulmonary lesions are characterized by fibrosis. There can be no doubt, however, that when the silicotic becomes an overt, clinical case of tuberculosis it means that the infection has gained the upper hand, and the expectancy of life is then quite short.

All authorities agree that tuberculosis as a complication of pneumonoconiosis runs an atypical course and is much more difficult of clinical detection than ordinary, non-occupational tuberculosis. Thus, the pneumonoconiotic modification of the disease commonly occurs at a later age period than is usual, that is, in middle or advanced life, and in persons who generally have no constitutional or hereditary predisposition; the sputum is not so copious nor as likely to contain tubercle bacilli; hemoptysis is rare; fever and nightsweats are usually absent; emaciation is little in evidence and the localization of pulmonary lesions is seldom apical (Collis, 1915).

Similarly, the pathologic picture differs materially from that of uncomplicated tuberculosis. The coniophthisic lung is typically dry, dusty and fibrotic, often with little or no evidence of caseation or the usual cellular reactions of tuberculosis. It is a pathologic process which runs to an unusual degree of fibroid healing and at the same time to an unusually wide dissemination. While this is the classical picture, it must be remembered that pneumonoconiotic tuberculosis, like ordinary pulmonary tuberculosis, is a protean disease capable of wide variations in its anatomic manifestations.

Pneumonia as a Complication of Pneumonoconiosis. Acute respiratory infection is a common sequel to dust inhalation. Collis (1915) points out "the excessive mortality from pneumonia occurs at those earlier age periods which represent initial exposure." If and when infection of the pneumonoconiotic lung takes place, the individual is at a distinct disadvantage, for the blocked lymphatics prejudice the lung's ability to deal with infection (Mavrogordato, 1922). Strachan (1930) states that in cases with prolonged exposure to mine dust, though the specific lesions of silicosis may not yet have developed, an acute pulmonary infection, such as lobar pneumonia, is often followed by non-resolution, organization and fibrosis. Haythorn (1918) has shown that a simple pneumonoconiosis of anthracotic type has a very unfavor-

able influence on the course of an attack of pneumonia, impeding resolution and leading to serious complications.

Factors Relating to the Tuberculous Affinity of the Dusty Lung. An excessive incidence of tuberculosis in relation to pneumonoconiosis might be expected on the following grounds: They are both inhalation diseases; they have a common portal of entry and a common predilection to localize and spread in the pulmonary lymphatic apparatus (Shattock, 1914); both are dealt with by the same protective mechanism, namely, the dust phagocyte (Gardner, 1924). Dust particles act as carriers, facilitating the entrance of the ubiquitous tubercle bacillus into the lung (Landis, 1919). People exposed to dust hazards frequently work under wet conditions which favor the survival and transference of infective organisms (Mavrogordato, 1926; Beattie, 1912). People exposed to dust hazards are also frequently exposed to a greater risk of infection because of open cases of tuberculosis among their fellow workmen (Mavrogordato, 1926). A large proportion of persons exposed to dust hazards work underground where the survival and dissemination of pathogenic organisms is facilitated because of moisture and warmth and the absence of sunlight (Landis, 1919). Cesa-Bianchi (1913) caused guinea pigs to inhale various factory dusts, including talc, coal dust, cement and sand, then infected the animals with a strain of tubercle bacilli of low virulence; all his dusted animals, regardless of the type of dust used, died of pulmonary tuberculosis, while the controls were unaffected.

Gye and Kettle (1922) demonstrated that silica-soaked necrotic tissue was a medium favorable to the growth of tubercle bacilli *in vivo*. Kettle (1932) produced subcutaneous lesions with silica, shale, clay and asbestos dusts, then showed that tubercle bacilli injected intravenously localized and multiplied inordinately in these lesions while the presence in the tissues of carborundum, wellingtonite, iron oxid, carbon, coal, marble, silica-free mine dust and iron-coated silica was apparently a matter of indifference to the organisms. Price (1931) found sodium silicate definitely accelerated the growth of tubercle bacilli *in vitro*.

Gardner (1924) found that a previous exposure of animals to more or less prolonged inhalation of granite, carborundum and marble dusts rendered the lungs more susceptible to subsequent infection with the tubercle bacillus. He regarded this effect as due to obstruction of the pulmonary lymphatics. Of even greater significance as regards its application to the problem of human coniotuberculosis was Gardner's later work (1929), in which he tested the effects of various dusts on partially healed tuberculous lesions in guinea pigs' and rabbits' lungs; these experiments demonstrated that 73.6% of quartz-dusted, 31.8% of carborundum-dusted and 26.3% of granite-dusted animals showed marked reactivation of their tuberculous lesions, while most of the control animals and those dusted with marble and soft coal went on to complete healing. On the basis of these results Gardner thinks it likely that in the majority of cases coniotuberculosis represents an endogenous reinfection resulting from the reactivation (by silicious dust) of old, quiescent lesions so commonly present in the average, white, adult individual.

Willis (1922) found that experimental tuberculosis developed somewhat more extensively in the lungs of animals previously exposed to coal dust than in those of normal animals.

Mavrogordato (1926) showed that guinea pigs and rats which had inhaled mine dust were prone to develop pulmonary tuberculosis following intraperitoneal inoculation with tubercle bacilli, whereas control animals were not similarly affected by such an inoculation. Coal dust inhalations did not protect guinea pigs from developing pulmonary tuberculosis after intraperitoneal inoculation of tubercle bacilli. As regards coal dust, the results of Cesa-Bianchi, Willis and Mavrogordato are at variance with those of Wainright and Nichols (1905), in whose hands this type of dust protected rabbits' lungs from the ravages of tuberculosis.

There is more or less general agreement that coalminers suffer less from tuberculosis than the average of occupied males. The experimental work of Cummins and Weatherall (1931) would provide some explanation of this finding in that they were able to show that anthracite coal dust has the power of adsorbing the active principle of tuberculin.

The Diagnosis of Pneumonoconiosis. It is perhaps illustrative of the difficulty often encountered in establishing the presence of pneumonoconiosis that practically all who have to do with the diagnosis of the condition emphasize the importance of taking into account all available information concerning a case before an opinion is expressed. In many instances an accurate diagnosis may be arrived at during life from a consideration of the occupational history, the physical and roentgenologic findings. And after death a naked-eye examination of the lungs will often suffice to establish the case. Pathologists in the South African mining fields contend that in cases which come to autopsy it is possible to give a definite opinion regarding the degree of silicosis present from the appearances found in the macroscopic specimen alone; in fact, it is only rarely that resort is had to microscopic analysis (Strachan and Simson, 1930). But in Europe and America such confirmatory evidence as may be obtainable from laboratory investigations is often required for compensation purposes.

One swallow does not make a summer, no more than one nodule will make a case of silicosis. There must be visible and palpable fibrosis, and the lesions must be present in such numbers that, on the average, at least one will appear in each 5 cm. squared of the divided lung substance (Watkins-Pitchford, 1927).

The greatest difficulty encountered by the pathologist is to assess the rôle of dust in complicated cases, especially those in which there is much fibrosis, part or all of which may be due to causes other than dust. The changes characteristic of the early phases of pneumonoconiosis should not be overlooked in arriving at a diagnosis. Choking and thickening of the pulmonary lymphatics by dust particles is a necessary preliminary to the more advanced lesions (Mavrogordato, 1922) and provides an easily recognizable criterion of the presence of pneumonoconiosis, yet sometimes it seems to be overlooked in the pathologic analysis of certain complicated cases, and often enough more importance is attached to the chemical assay of the tissue than to the condition of the lymphatics. It is hardly to be expected that dust could be accountable for extensive changes in the parenchyma of the lung if it has not yet produced the lymphatic choking which is recognized to be its initial effect. There is perhaps too great a tendency to regard lung fibrosis by and large as a specific effect of dust. Fibrosis is essentially a non-specific change and may be called forth in the lung by any number of different agencies, but especially by organizing

pneumonia, chronic interstitial pneumonia (Lauche, 1928) and tuberculosis. Gardner (1932) believes chronic pneumonias to be quite common in man as well as animals, and Mavrogordato (1926) and Strachan and Simson (1930) have stressed the frequency with which this condition complicates pneumonoconiosis. Kettle (1934) has shown very convincingly how closely the lesions of pneumonoconiosis may be simulated by non-occupational fibroid phthisis.

Thus, when ordinary histologic methods of analysis fail to make the necessary distinctions, recourse is had to methods of demonstrating the amount and character of foreign particulate matter present in the lesions in question.

The polarizing microscope is a useful adjunct for demonstrating birefringent mineral particles in histologic preparations. It is frequently possible to gain a rough idea of the amount and distribution of silicious particles, and thereby to establish the presence of a dust factor by this means alone. The advantages and limitations of the instrument are set out by Watkins-Pitchford and Moir (1916) and Belt (1929).

More accurate estimations of the dust content of the lung tissue may be obtained by chemical assay of the "total silica" present. As has been pointed out elsewhere, "total silica" is simply an expression of the amount of the element silicon and gives no indication as to what form of silicon compound or compounds were present. But since most of the harmful dusts are either oxids of silicon or silicates, the "total silica" is a serviceable index of the dust factor in a given specimen of diseased tissue. The "total silica" content of normal lung varies from 0 up to 0.2% of the dry weight (King, 1928). Figures in excess of the normal range may, therefore, be taken to indicate dust disease (Sladden, 1933; McNally, 1933; Kettle and Archer, 1934), but will not aid in distinguishing between silicosis and silicatosis.

There is one possible fallacy worthy of mention in the interpretation of "total silica" assays. Woskressensky (1898) demonstrated that the "total silica" content of normal tracheobronchial glands increases with age, from *nil* in the newborn to the surprisingly high proportion of 34 to 55% of the ash in elderly individuals. This is simply the result of life-long inhalation of ordinary house and street dusts, which are partly constituted by clay and sand particles. Confirmation of Woskressensky's early observations will shortly be published by Belt and King. Thus all ordinary adults have a silicosis or a silicatosis as well as an anthracosis of the tracheobronchial lymph glands and to some extent of the pleura as well. In the ordinary course of events, these "normal" dust deposits are confined to lymph glands and pleura and do not locate in the substance of the lungs. If, however, there are scars in the lung parenchyma, as from a childhood tuberculous infection, the "normal" dusts will collect around such a scar, as witness of which it is observed that old tuberculous lesions are invariably surrounded by a zone of anthracotic pigmentation. Therefore, if peribronchial glands or disproportionately large areas of pleura or localized childhood scars be included, as might easily happen, in the block of suspected lung submitted for chemical assay, the resulting "total silica" estimation will likely include considerable quantities of "normal" silicious dust, and a high percentage of "total silica" in the ash may, therefore, be misinterpreted as indicating silicosis or silicatosis. For this reason it is necessary, if reliance is to be placed on chemical assay

as an aid in diagnosis, to submit several blocks of the suspected lung, and to know from what part of the lung each block was taken.

A third laboratory method of investigating the mineral content of tissues is microincineration, described by Policard (1929), Schultz-Brauns (1929), Scheid (1932) and others; it is a modification of the early technique of Greenhow (1865), and has the advantage of enabling a microscopic study of the physical relationship of dust deposits to the tissue changes. It is possible by this means to determine the dust content of individual lesions more accurately than by the use of the polariscope on ordinary histologic preparations. From an ordinary paraffin block of tissue, serial sections 5 or 6 μ thick are cut in groups of 3; of each group, 1 is stained with hematoxylin and eosin in the usual way, while the other 2 are mounted unstained on glass slides and heated for an hour to 500° C. in a specially constructed oven. The heating drives off all the organic constituents of the tissue section, leaving the inorganic and mineral residue lying *in situ*. One of the ashed sections is then treated with concentrated hydrochloric acid, which removes calcium, iron and phosphorus compounds, leaving silica and silicates as well as a few other substances which occur only in traces. Then by comparing this slide with the stained section the deposits of residue are readily related to the histologic detail. This procedure will demonstrate prettily the amount of silicious material in a given lesion; it does not, however, always serve to distinguish infective from non-infective dust lesions (*contra* Irwin, 1934) for tuberculous lesions in the coniotic lung, for example, are often heavily strewn with silicious particles (Gardner, 1920; Belt, 1929). By microincineration it is possible to exclude silicious dust as the cause of certain lesions, for if there is any silicious material present in a lesion, microincineration is sure to demonstrate it, and in the absence of any such material the lesion must obviously owe its existence to some other agency. Microincineration is also of assistance in judging whether infective lesions are antecedent to or coincidental with dust exposure. If, in a coniophthisic lung, it can be shown that foreign particulate matter is scattered through tuberculous lesions, then the case may be regarded as one of coniotuberculosis; but if, on the other hand, tuberculous lesions or fibroid lesions without evidence of active tuberculosis are shown to contain no foreign particulate matter, then such lesions are to be regarded as belonging to a process which antedated the dust exposure; for it has been established that any infective lesion of the lung, tuberculous or otherwise, which develops during the course of or following dust exposure will contain appreciable quantities of the dust, because dust-laden phagocytes take an active part in any superimposed inflammatory reaction (Gardner, 1920).

Summary and Conclusions. From a review of the present knowledge of pneumonoconiosis it may be concluded:

1. There is no conclusive evidence to show that silica has a specific action on the tissues.

2. Certain of the silicates and perhaps other substances may produce similar if not identical effects.

3. Infection, and especially tuberculous infection, is a more serious factor in the development of the disabling pneumonoconioses than dust *per se*.

4. Dust modifies pulmonary tuberculosis in a twofold manner; it

increases the fibrous response, thus promoting chronicity, and at the same time it increases the tendency of the infection to spread.

5. The so-called "silicotic nodule" has probably never been reproduced experimentally except by the synchronous inoculation of tubercle bacilli with dust.

6. The "silicotic nodule" is probably always a tuberculous lesion, modified by dust.

7. Chemical assay of suspected tissues is open to the criticism that it does not reveal the proportion of silica to silicates.

8. There is probably no such thing as acute silicosis.

9. Evidence regarding the action of coal dust on the tissues and its influence on tuberculous infection is conflicting.

T. H. B.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,
AND
GEORGE W. McCOY, M.D.,
DIRECTOR OF NATIONAL INSTITUTE OF HEALTH, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

NEWER ASPECTS OF TYPHUS FEVER.

Typhus and typhus-like diseases have in recent years attracted considerable attention in various parts of the world, and out of the

studies that have been prosecuted there has developed a new orientation on the subject, largely as a result of the work of American observers. The study of the infection in the United States has been of particular interest. The evidence indicates that typhus is quite prevalent in some of the states bordering the Gulf of Mexico and in those of the South Atlantic group—in other words, from Texas to Maryland, with scattered cases along the remainder of the Atlantic Seaboard. For many years the knowledge of the transmission of typhus—based on observations made in the Old World—had been regarded as quite satisfactory. It was regarded as an infection of man, always derived from man through the body louse, the louse having fed on and having been infected from another case of the disease. Some 10 years ago, to be sure, Maxcy cast some doubt on the views of transmission then held by pointing out differences in epidemiology between typhus as known in Europe and typhus as it occurs in the southern United States. Briefly, he showed that typhus in the United States was a summer and fall disease as against its prevalence in winter and spring in Europe, that it apparently never spread from person to person, that it was not particularly prevalent in institutions—indeed, that institutions had a noteworthy immunity—and, finally, that the victims rarely, or never, presented evidence of infestation with body lice. Within the past 3 years, Dyer and his associates, of the United States Public Health Service, and Mooser and his associates, in Mexico, have studied the subject intensively from the point of view of transmission and present an explanation of the facts observed by Maxcy and others that involves an entirely new conception of the mode of transmission. In these studies, suspicion was attracted first to rat fleas and to the rat, since it had been observed that in endemic foci of the disease rat-infested premises often were associated with the development of typhus infection. Laboratory examination of rats and rat fleas taken from such premises actually showed the presence of the typhus virus. The connecting link between the typhus-infected rat and man is apparently the flea (*Xenopsylla cheopis*), which it so happens is also the carrier of the bubonic type of plague.

Flea transmission was proven by the rat-to-rat transfer of infection by means of the flea. Not only do these studies offer an explanation of the observed facts in relation to typhus as it occurs *endemically* in the United States and in other parts of the world, but they justify an entirely new hypothesis to account for the prevalence of *epidemic* typhus. Briefly, this view is that in many communities typhus lies relatively dormant as an infection among rodents, propagated among them by fleas, and is communicated occasionally to man through the same parasite. If this transfer of the infection to man should occur in a louse-infested population, and other conditions are favorable, the disease then may spread among the human population as a louse-borne infection. This explanation seems to meet the facts with respect to epidemic typhus.

It is obvious that if the views referred to above are sound (and there are many reasons for believing that they are) our efforts to combat typhus—hitherto directed entirely against human body lice—must take account of the rat and his parasites.

Rickettsiæ, constantly associated with the disease in animals and in

lice, are also present in typhus-infected fleas. These bodies, or bodies indistinguishable from them, have been propagated in tissue cultures, although they have resisted efforts at cultivation in artificial media. The recent immunologic studies of Zinsser have furnished additional evidence of their etiologic significance.

The clinical aspects of typhus as it occurs in the United States are of special interest, since cases are often overlooked. The onset is usually sudden, with chill and fever, aching pains and often with pronounced, persistent headache. The fever lasts about 14 days, defervescence usually taking place by rapid lysis. On about the fifth day a rash appears which may be scanty or abundant and which usually develops first over the lower ribs or upper abdomen. It consists of small discrete red macules, not shotted and not itching. In severe cases it may spread to practically the whole of the cutaneous surface, but usually spares the hands and feet. The face and neck are seldom involved. The rash usually begins to fade 4 or 5 days after its appearance.

An important aid in diagnosis is derived from serologic investigation, since the blood serum in this disease almost invariably shows a positive reaction with the well-known strain of *B. proteus* in general use for the diagnosis of members of the typhus group of infections. This serologic test, of great value though it is, does not serve to differentiate the condition from spotted fever of the Rocky Mountain type, and possibly other closely associated diseases of the same type.

The prognosis of typhus as it occurs in the United States is, in general, very good. The death rate certainly is not more than 1 or 2%.

Treatment appears to be symptomatic, with special emphasis laid on the giving of adequate amounts of fluid and the maintenance of general nutrition. Convalescence usually is fairly prompt.

G. W. McC.

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